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SOME CLINICAL AND ETIOLOGICAL ASPECTS

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CHAPTER I

INTRODUCTION AND OUTLINE OF INVESTIGATIONS ON FAMILIAL STRIO-PALLIDO-DENTATE CALCINOSIS

1. STRIO-PALLIDO-DENTATE CALCINOSIS

1.1 Definition

Strio-pallido-dentate calcinosis (SPDC) is the occurence of symmetrical calcifications in the basal ganglia and/or dentate nuclei (2, 68, 100). Other frequently used names include cerebral calcinosis, basal ganglia calcification and lenticulodentate calcification (47, 61, 68). This disorder has often been called Fahr's disease, suggesting a recognizable clinical syndrome (34, 68, 75). However, many SPDC patients have been reported who lacked consistent symptoms (16, 61, 65, 80, 117). Furthermore, Fahr (32) was not the first to describe SPDC. It had already been reported in 1856 by Virchow (116).

1.2 Neuropathology

Neuropathological studies on the brain of SPDC patients revealed stonelike masses in the basal ganglia and dentate nuclei (68). Under the light microscope, drop-like products are visible in and around the walls of the arteries, capillaries and veins in the basal ganglia and dentate nuclei as well as in the cortex, subcortical white matter and radiation of the corpus callosum (25, 68, 86). Electron microscopic studies have shown that these products can be found within the basal membranes of the blood vessels (41). They are composed of 140-400 Å translucent filaments (acid mucopolysaccharides) in which dark segments of 40-80 Å subunits (calcium deposits) are found (41).

X-ray spectrographic methods have shown that the calcium deposits are composed of hydroxy-apatite (15, 77). Histochemical techniques as well as infra-red, x-ray and laser spectrometry, have demonstrated that elements as well as calcium may be stored: iron, magnesium, zinc, copper, manganese, cobalt and silicium (14, 20, 26, 30, 63, 68). The presence of calcium-containing products in the brain is suggested by presence of hematoxylin-positive material (54). However, hematoxylin is not a specific calcium identifying agent. When calcium

deposits have to be demonstrated, specific calcium identifying agents (alazarine red S) or microprobe techniques have to be used (30, 67, 68, 93). Hematoxylin positive material in and around the blood vessels, in which calcium can not be demonstrated by specific calcium identifying techniques, is often called "pseudocalcinosis" (10, 54). While this "pseudocalcinosis" has been found in about 70% of the routine biopsies conducted on the aged (91, 104), it is seldom found in young people (104). This suggests that "pseudocalcinosis" is an age related process (68, 77). The neuropathological sign 'pseudocalcinosis' probably represents a physiological process. The neuroradiological sign "SPDC" however, seems to represent a pathological process.

1.3 Neuroradiology

Extensive SPDC can be diagnosed on skull radiograms. The calcifications in the basal ganglia can be seen on the lateral and P-A views. The calcification in the dentate nuclei is commonly obscured in the lateral views by the mastoid bones, but is often well demonstrated in the Towne's projection (92). The incidence of SPDC seen on skull radiograms has been studied is a retrospective survey of 31 years experience at the Mayo Clinics, showing SPDC in 38 patients (77).

Computed tomography (CT) scanning is 5-15 times more sensitive in detecting cerebral calcifications than plain skull radiograms (61, 80). Nevertheless, SPDC is not frequently diagnosed with this technique. The occurence of calcifications in the basal ganglia varies between 0.5 and 1.6%; in 0.05% of these cases calcifications in the dentate nuclei are also present (16, 61, 80, 100).

The time in which SPDC originates is not exactly known. In radiological studies the shortest time has been reported to be 31 days (102). The minimum diameter of a calcification which can be detected by a CT scanner depends upon many factors. These include the properties of the used CT scanner, the amount of calcium in the calcification, the extent of the calcification and the partial volume effect (see appendix).

1.4 Pathophysiology

The mechanism of calcification in normal and pathological circumstances is related to changes in the tissue cells and extracellular matrix (13, 82, 84, 99, 114).

1.4.1 General aspects of mineralisation

To form insoluble crystalline material, ions or groups of ions must come together with sufficient collision energy and with the right orientation to form a "critical nucleus", the smallest stable combination of ions with the structure of the crystalline material that can remain in a solution. Nucleation - formation of this critical nucleus - requires energy. Once the critical nucleus is present, the addition of more ions and/or ion clusters to the critical nucleus requires less energy than the original formation of the critical nucleus. Crystal growth or proliferation proceeds by a variety of mechanisms and can be facilitated by the presence of critical nuclei or materials that resemble critical nuclei (epitaxy). Nucleation and growth can be promoted by increasing the activity of ion products, and/or by removing inhibitors (13, 99).

1.4.2 Factors controlling biological calcification

Despite extensive research in the last ten years, the exact nature of the process of biological calcification is not known. There are many factors found, that are involved in controlling biological calcification: (13, 81, 84, 99, 114).

a. One of the first steps in biological calcification is probably the transformation of amorphous calcium-phosphate into crystalline hydroxy-apatite - $Ca_{10}(PO_4)_6(OH)_2$-. In this transformation dehydration plays an important role (114).

b. Before a tissue calcifies, the extracellular framework must be converted from a noncalcifying to a calcifying matrix. There are two main theories on the biochemistry of formation of a

calcifiable matrix (114). One theory is that calcium is bound by tissue proteins and in the process so changes in structural configuration as to produce a nucleation center. The other theory is that phosphate is bound by collagen so as to produce a nucleation center.

c. Specialized tissue cells are involved in the initiation and control of calcification by means of mitochondria and matrix vesicles. The mitochondria provides storage sites for calcium and phosphate. Depletion of ATP, i.e. when aerobic glycolysis ceases, is supposed to induce the release of calcium and phosphate from the mitochondria. It is also possible that the release of calcium and phosphate from the mitochondria is secondary to the calcification of the matrix. Once the initial mineral is deposited, the decrease in oxygen tension and the concomitant cessation of the glycolytic cycle could result in a release of calcium and phosphate from the mitochondria or the cells of calcifying tissues, accelerating the mineralization process (13).

   Matrix vesicles are phosphate rich, membrane-bound bodies localized in the matrix. They are sometimes formed by intact cells or can also appear as a result of cellular degeneration. Their membranes contain acid phospholipids which have a high affinity for calcium. These phospholipids can form complexes with calcium and phosphate which promote hydroxyapatite formation and growth (13, 81, 84, 114).

d. The transport and binding of calcium to protein is regulated by many enzymes: alkaline phosphatases, acid phosphatases, inorganic phosphatases, proteases, acid hydrolases and carbonic anhydrases (13, 114).

e. Growth of apatite deposits can be prevented by many inhibitors, including heparin, proteoglycans, pyrophosphates, phlorizin, iodoacetate, fluoride, cyanide, dinitrophenol, beryllium, polyphosphates and diphosphonates (13, 84, 99, 114). The inhibition of calcification has been studied in calcifying arteriosclerosis, diffuse interstitial pulmonary calcification, tumoral calcinosis and calcinosis cutis (13, 99, 114).

There are many unknown factors that can be added to those mentioned above that probably can determine whether and where calcifications occur.

1.4.3 Factors involved in the origin of SPDC

The question of which of the above mentioned factors are involved in the origin of SPDC has not been studied in detail. The early proximity of calcifications to vascular walls led some investigators to the assumption that a vascular component plays an important role in the origin of SPDC (68, 86). Others (10, 16, 41, 66) were impressed by frequently observed disturbances of the calcium-phosphate metabolism in SPDC patients. These researchers suggested that local changes of calcium concentrations could alter vascular permeability resulting in the permeation of phosphate rich serum, which in turn could provoke calcium-phosphate deposits.

1.5 Disorders associated with SPDC

There are many different disorders associated with SPDC. Since the use of CT scanning the number of disorders associated with SPDC has increased. SPDC has not only been diagnosed in neurological disorders, but also in many other disorders, covering many fields of medicine. Consequently, it is impossible to produce a complete list of disorders in which SPDC has been reported.
After reviewing the literature on SPDC, we have subdivided the most frequently reported disorders associated with SPDC into three groups, according to the localization of the calcifications. Each of these groups is subdivided into "familial" and "sporadic" disorders. The three groups include:

a. Disorders associated with symmetrical calcifications only in the basal ganglia (table 1).
b. Disorders associated with symmetrical calcifications only in the dentate nuclei (Table 2).
c. Disorders associated with calcifications in both basal ganglia and dentate nuclei (Table 3).

Autosomal dominant:

- autosomal dominant idiopathic SPDC (5, 12, 89, 126).
- autosomal dominant idiopathic hypoparathyroidism (3).

Autosomal recessive:

- autosomal recessive idiopathic SPDC (88, 126).
- Cockayne's syndrome (42).

Sporadic disorders

- disturbed Ca-P metabolism:
  - hypoparathyroidism (-, 21, 27, 29, 31, 36, 46, 56, 68, 77, 101).
  - hyperparathyroidism (90).
- intoxications:
  - post-radiation-therapy (63, 96).
  - post-methotrexate therapy (33, 55, 76).
  - leukemia (106).
- hypoxaemia:
  - cerebrovascular accidents (16, 61, 89, 109).
  - carbon monoxide poisoning (6, 60, 61, 68).
- infections:
  - cytomegalovirus (6, 68, 118).
  - toxoplasmosis (6, 68).
- phacomatosis:
  - tuberous sclerosis (6, 68, 109).
  - Sturge-Weber (6, 68, 119).
- others:
  - idiopathic SPDC (7, 25, 32, 38, 45, 59, 61, 68, 78, 82, 105, 115, 117).
  - mitochondrial encephalomyopathies:
    - Kearns-Sayre (98, 103).
    - unclassified (79, 107).
  - chromosomal abnormalities:
    - Trisomy 21 (51, 74, 79).

Table 1.

Disorders associated with symmetrical calcifications found only in the basal ganglia.

Table 2.
Disorders associated with symmetrical calcifications found only in the dentate nuclei.

Idiopathic SPDC (58, 62).
Lead Poisoning (112).

Table 2.

Disorders associated with symmetrical calcifications found only in the dentate nuclei.

Table 3.
Disorders associated with symmetrical calcifications in both basal ganglia and dentate nuclei.

Familial disorders:

- autosomal dominant:
  - autosomal dominant idiopathic SPDC (12, 129).
  - autosomal dominant idiopathic hypoparathyroidism (13).
- autosomal recessive.
  - autosomal recessive idiopathic SPDC (2, 9, 9, 22, 37, 72, 73, 88, 110, 124).
  - autosomal recessive idiopathic SPDC -"plus" (39, 46, 73, 113).
  - Cockayne's syndrome (42, 53, 108).

Sporadic disorders:

- idiopathic SPDC (28, 52, 57, 61, 68, 69, 87, 95, 104, 117, 119).
- hypoparathyroidism (8, 35, 36, 50, 101).

Table 3.

Disorders associated with symmetrical calcifications in both basal ganglia and dentate nuclei.

Because CT scanning ensures a better localization of cerebral calcifications than plain skull radiograms, many patients now summarized in table 1 on account of their skull radiograms would be summarized in table 3 had CT scanning been performed.

Familial SPDC has been described as having either an autosomal dominant or an autosomal recessive mode of inheritance (12, 68). The autosomal dominant inherited disorder is reported to be associated with autosomal dominant hypoparathyroidism (idiopathic hypoparathyroidism, pseudohypoparathyroidism and pseudo-pseudohypoparathyroidism) (68, 83). Whether SPDC occurs in autosomal recessive or X-linked hypoparathyroidism is unknown because the incidence of SPDC in these forms of familial hypoparathyroidism has not been reported as far as we know.

In many of the literature recorded SPDC patients no evidence could be found of a disturbed Ca P metabolism, toxic and anoxic factors, infections, phacomatosis, mitochondrial disturbances, chromosomal abnormalities or Cockayne's syndrome. We have these patients classified as "idiopathic SPDC". According to Troost et al (113) the idiopathic SPDC patients described by Laubenthal (64) and Hallervorden (46). Melchior (73), D'Hoore (28) and Troost (113) represent a separate entity, as they show in addition to SPDC, psychomotor retardation, microcephaly, cerebral neuronal calcification and hypoplasia of the cerebellum. According to Goutieres (39) the idiopathic SPDC patients described by Jervis (52), Lyon (69), Goutieres (39), Hallervorden (46) and Melchior (73) also represent a separate entity as they share SPDC, progressive encephalopathy, brain atrophy and leukodystrophy with persistent cerebrospinal fluid lymphocytosis as characteristic features. We have classified idiopathic SPDC patients belonging to the entity of Troost (113) and/or Goutieres (39) as idiopathic SPDC-"plus". The symptoms of the patients with autosomal recessive idiopathic SPDC "plus" (39, 46, 73, 113) are recorded in fig. 1. The symptoms of the patients with autosomal recessive idiopathic SPDC and Cockayne's syndrome will be mentioned, respectively, in chapters III and IV.

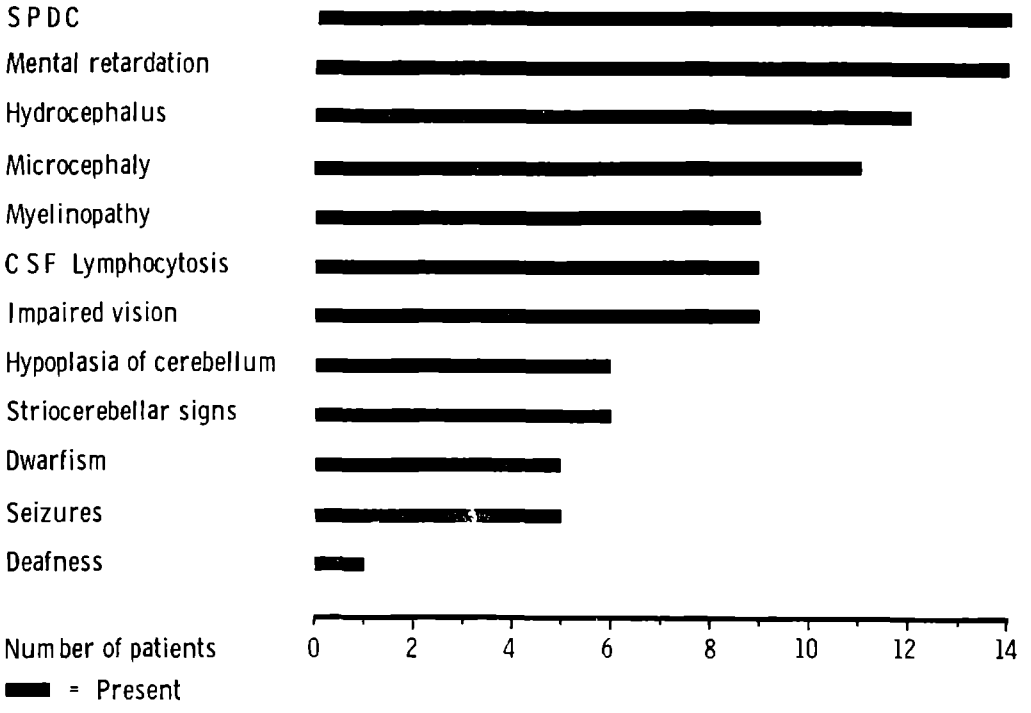

Fig. 1 Symptoms in fourteen previously reported patients (39, 46, 73, 113) with autosomal recessive idiopathic SPDC-"plus".

The observation that 70-80% of the SPDC patients diagnosed on skull radiograms showed a disturbance in the calcium-phosphate metabolism suggested that a disturbed calcium-phosphate metabolism plays an important role in the origin of SPDC (68, 72, 88). Sachs et al (101) found that 93% of the patients with known hypoparathyroidism showed CT scan-diagnosed SPDC. However, in only about 10% of randomly CT scan-diagnosed SPDC patients could a form of hypoparathyroidism be diagnosed (110).

The presence of SPDC in the Kearns-Sayre syndrome (103) could be a consequence of an unknown metabolic disorder which also produces the other signs of this syndrome. The presence of SPDC in the Kearns-Sayre syndrome could also be explained by the association of hypoparathyroidism with the Kearns-Sayre syndrome (48, 94).

2. PARATHYROID HORMONE AND ITS FUNCTION

2.1 Parathyroid hormone

Parathyroid hormone (PTH) is a single chain polypeptide of 84 amino acids produced in the parathyroid gland (43). The PTH molecule is partially broken down in the liver, bones and kidneys. Some of the PTH fragments probably have biological activity (44). Serum PTH concentrations can be measured by radio-immuno-assay (RIA) (18). However, the general inavailability of homologous (i.e. human) PTH antiserum, the immunoheterogenity of circulating PTH and its fragments, in addition to the lack of standardized reagent and assay procedures, ensure that interlaboratory assay results are divergent and thus have to be interpreted very carefully (18).

2.2 Extracerebral effects of parathyroid hormone

Studies on the function of PTH have been performed mainly in extracerebral tissues where it has been shown that PTH is the principle regulator of calcium concentration in extracellular fluid (1).

Its mechanism of action is mainly mediated by its activating effect on the extracellular membrane-bound adenylcyclase complex: it activates the intracellular transformation of adenosine triphosphate into cyclic adenosine monophosphate (cAMP), a second messenger, which stimulates specific properties of a cell (17, 23).

In the renal proximal tubular cells, PTH stimulates the adenylcyclase system, resulting in a decrease of the renal threshold for phosphate (TmP/GFR, see reference 11). A decrease in the extracellular phosphate concentration stimulates the hydroxylation of 25 OH cholecalciferol into 1,25 $(OH)_2$ cholecalciferol in the interstitial renal cells. The hydroxylation might also be stimulated directly by PTH. 1,25 $(OH)_2$ cholecalciferol in turn stimulates the intestinal absorption of calcium and increases serum calcium concentration. In the bones, PTH is involved in bone turnover by the stimulation of calcium mobilisation from the bone cells. This results in an increase in serum calcium concentration. An increase in calcium concentration decreases PTH secretion from the parathyroid gland (fig. 2) (1, 71).

2.3 Cerebral effects of parathyroid hormone

Many different neurological disturbances, including mental retardation, psychosis, pyramidal, extrapyramidal and cerebellar signs. EEG disturbances and SPDC, are associated with hypoparathyroidism (36). Except for SPDC, these signs of cerebral dysfunction are also associated with hypoparathyroidism (36). This suggests that PTH influences cerebral function. It is probable that this influence is mainly indirect by affecting the Ca-P metabolism. For instance, the observation that seizures in parathyroid-ectomised patients are controlled by correction of the serum Ca levels by administering Ca (36) suggests that the seizures are the consequence of low serum Ca levels and not the consequence of low PTH levels. The additional observation that SPDC remains present in these patients suggests that other factors influence the presence of SPDC.

As far as we know, a direct influence of PTH on cerebral function has not yet been demonstrated, neither has the presence of cerebral

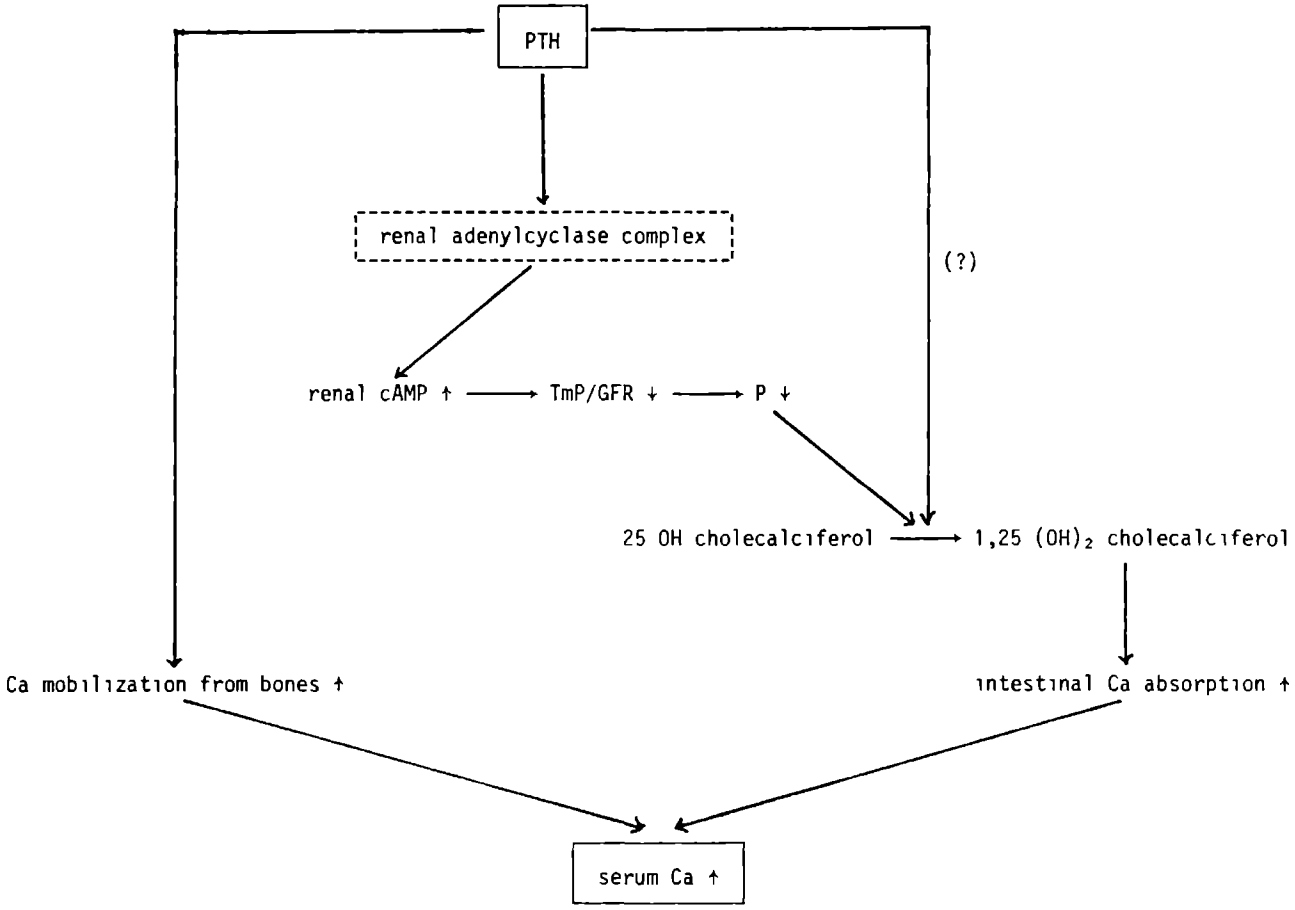

Fig. 2 Schematic representation of the influence of parathyroid hormone on the calcium-phosphate metabolism

PTH receptors been shown. Recently, cerebral receptors of 1,25 $(OH)_2$ cholecalciferol and calcitonin have been demonstrated (97, 111). The effects of their stimulation are still unknown.

3. OUTLINE OF THE STUDIES ON FAMILIAL STRIO-PALLIDO-DENTATE CALCINOSIS

3.1 History

The investigations on familial SPDC were performed after we had been confronted with a family with autosomal dominant SPDC and two families with autosomal recessive SPDC. Reviewing the literature, we concluded that the symptomatology and the etiology of SPDC were greatly unknown.

The most recent extensive studies on SPDC had been published about 15 years ago (68). Since that time many new techniques (CT scanning, evoked potentials, histochemical and electron microscopic techniques to study muscle and nerve biopsies) have been developed to study neurological signs. We wondered if these techniques could help obtain more knowledge about the symptomatology and etiology of SPDC.

From the literature on SPDC it was evident that many exogenous and endogenous factors are involved in the origin of SPDC. The only known endogenous factor is a disturbance somewhere in the calcium-phosphate metabolism. Endogenous factors play an important role in the etiology of familial disorders. In autosomal recessive disorders the endogenous factor is a defective enzyme produced by a gene defect. Thus it may be possible that autosomal recessive SPDC is associated with a defective enzyme by which a disturbance in the calcium-phosphate metabolism is produced. To test this hypothesis we studied calcium-phosphate metabolism in our patients with autosomal recessive SPDC.

Calcium-phosphate metabolism is greatly influenced by parathyroid hormone. Because the parathyroid hormone seemed to influence cerebral functions we were especially interested in methods of

studying this influence. However, we were not able to study this influence of PTH on cerebral functions with conventional methods. In analogy with the PTH stimulated renal adenylcyclase complex, we hypothesized the presence of a cerebral PTH-responsive adenylcyclase complex. We tested this hypothesis in three healthy persons and studied the function of this cerebral PTH-responsive adenylcyclase complex in a patient with autosomal recessive idiopathic SPDC and in a patient with Cockayne's syndrome.

3.2 Aim of the investigations

In our study we wanted to answer the following questions:

a. Is familial SPDC characterized by a specific entity of neurological signs?
b. Is a disturbance of the calcium-phosphate metabolism involved in the origin of autosomal recessive idiopathic SPDC and Cockayne's syndrome?
c. Can indications be found for the presence of a cerebral PTH-responsive adenylcyclase complex?
d. Is the function of the cerebral PTH-responsive adenylcyclase complex disturbed in autosomal recessive idiopathic SPDC and Cockayne's syndrome?

3.3 Performance of the investigations

In order to answer the above formulated questions we studied the neurological signs found in the affected members of a family with autosomal dominant idiopathic hypoparathyroidism, a family with autosomal recessive idiopathic SPDC and a family with Cockayne's syndrome. The results of our observations are described in chapters II, III and IV. The presence of a cerebral PTH-responsive adenylcyclase complex was investigated in another study. The results are recorded in chapter V. Calcium-phosphate metabolism and the cerebral PTH-responsive adenylcyclase complex were studied in patients with autosomal recessive idiopathic SPDC and in patients with Cockayne's

syndrome. The results of these studies are recorded in chapter VI. Chapter VII contains the conclusions of our investigations on some clinical and etiological aspects of familial SPDC.

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CHAPTER II

AUTOSOMAL DOMINANT IDIOPATHIC HYPOPARATHYROIDISM AND NERVOUS SYSTEM DYSFUNCTION: REPORT OF THREE CASES AND REVIEW OF THE LITERATURE

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SUMMARY

The neurological manifestations of idiopathic hypoparathyroidism in a father, his son, and his daughter are reported. In all three epilepsy was the first manifestation of the disease. Father and son also showed mental deterioration and striocerebellar symptoms; their CT scans revealed symmetrical calcification in the basal ganglia and dentate nuclei. The extent of this calcification increased during normocalcemia, which was produced by dihydrotachysterol therapy. This indicates that other factors than merely hypocalcemia influence the intracerebral calcifying process.

Somatosensory evoked potentials (SSEP) showed an abnormal nonspecific complex, indicating dysfunction of the cortical gray matter.

It is suggested that in the evaluation of idiopathic hypoparathyroidism one also must be beware of the possibility of epilepsy, mental deterioration, striocerebellar symptoms, intracerebral calcification and SSEP disturbances.

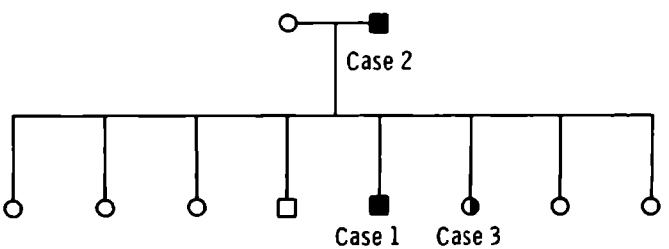
INTRODUCTION

Idiopathic hypoparathyroidism (IHPT) is a rare disorder characterized by hypocalcemia, hyperphosphatemia, and a low serum parathyroid hormone concentration, in the absence of renal impairment, malabsorption, osteomalacia, malignant disease, and a history of neck surgery or irradiation [15].

Neurological symptoms associated with IHPT are tetany, mental deterioration, epileptic seizures, signs of intracranial hypertension, pyramidal, extrapyramidal and cerebellar signs, psychosis, depression, calcification in the basal ganglia and dentate nuclei, and nonspecific disturbances in the electroencephalogram [10, 11, 12, 16, 17, 24, 25, 30, 32, 33, 37, 38]. Atypical myopathy has been reported in four sporadic cases of IHPT [31, 42] and axonal neuropathy in one case [14].

Familial IHPT has an autosomal dominant, autosomal recessive or X-linked mode of inheritance [1, 2]. Until now only five families have ever been described with autosomal dominant IHPT [1, 5].

We report here the clinical, neuroradiological, and electroneurophysiological findings in three members of a family with autosomal dominant IHPT and the histopathological findings of sural nerve and soleus muscle biopsies in one member of this family.



○ Normal.

■ Hypoparathyroidism; calcification in the basal ganglia and dentate nuclei.

◑ Hypoparathyroidism; normal CT scan.

Fig. 1. Pedigree of family

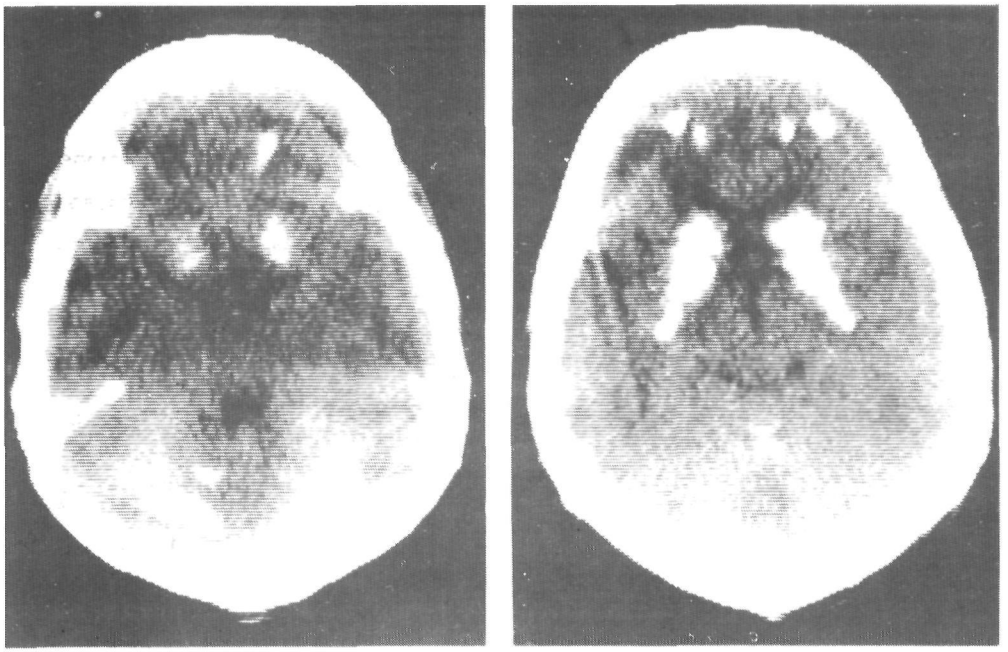


Fig. 2. CT scan of case 1 showing calcification in the dentate nuclei, vermis superior, basal ganglia, and cerebral white matter

CASE REPORTS

Family study

In all members of the described nonconsanguineous family (Fig. 1) general, physical, and neurological examinations were conducted. Serum calcium (Ca), phosphate (P), magnesium (Mg), parathyroid hormone (PTH), and calcitonin concentrations were measured and computed tomographic (CT) scanning was performed.

Except for cases 1, 2, and 3, all members had a normal history. Case 2 stated that his only sibling and his sibling's children are healthy. The father and mother of case 2, deceased at the time of this study, had an apparently normal history.

Case 1

From age 2 years onwards, case 1 had a history of generalized seizures, which could not be controlled by the usual anticonvulsant drugs. From age 15 he did not take any medication. There was alcohol abuse from age 14.

At age 16 he was admitted, unconscious, to the Department of Internal Medicine. Chvostek and Trousseau signs were strongly positive. Serum Ca concentration was 1.10 mmol/l (normal 2.20-2.60) and serum P 1.62 mmol/l (normal 0.76-1.24). Serum PTH was undetectable by radioimmunoassay. Intravenously administered PTH resulted in a normal decline of the elevated renal threshold for P (physiologically expressed as maximal tubular reabsorption correlated to the glomerular filtration rate, Tm/GFR). The serum Mg concentration was 0.49 mmol/l (normal 0.80-1.00), serum glutamic-oxaloacetic transaminase (SGOT) 62U/l (normal 5-15), serum glutamic-pyruvic transaminase (SGPT) 67U/l (normal 5-15), and the gamma-glutamyl transpeptidase (gamma GT) 200U/l (normal 6-36). Results of other relevant laboratory tests, including hematologic evaluation, renal, adrenal and pituitary function tests, calcitonin, alkaline phosphatase, lactate dehydrogenase, and electrophoretic analysis of serum proteins were normal. There was no evidence of malabsorption. Intravenously administered Mg. did not influence the serum Ca and P concentrations.

Radiological examination of the hands and long bones did not reveal any abnormality; skull radiograms showed calcification in the basal ganglia and cerebellum.

The diagnosis of IHPT was made and treatment with dihydrotachysterol was started. As a result, serum Ca concentration returned to a normal level, while serum Mg concentrations varied between 0.50 and 0.90 mmol/l. Epileptic seizures have not been observed since this treatment began.

At age 25, suffering from headache, he came to the Department of Neurology. A general physical examination showed that heart and lungs were normal, the liver was palpable two fingers below the costal margin and Chvostek and Trousseau signs were negative. There was a slight cogwheel rigidity and a masklike face. His gait was ataxic and there was a slight dysmetria. Reflexes and sensibility were normal. Plantar reflexes were

flexor. Ophthalmological examination revealed no abnormality.

Psychological examination. Groninger Intelligence Test (GIT) IQ: 94. The test profile was disharmonic (range 2.4 sigma; normal 2.0). Estimated IQ according to school performance: 110. Trailmaking test: 14 points (cutt-off point 13). Benton test: 5 items correct (expected score: 7 items). These test results are consistent with slight mental deterioration.
The electroencephalogram (EEG) showed slowing of background activity with generalized regular theta paroxysms. The electromyograms and the conduction velocities of motor and sensory nerves were normal. There were no signs of latent tetany [36] within 3 min of hypoxemia. Studies of somatosensory evoked potentials (SSEP), performed according to Colon et al. [7], showed an abnormal nonspecific complex [13], expressed by latencies P100, N145 and P200 (Table 1).
The skull radiograms showed a slight increase in intracerebral calcification. The CT scan revealed that this intracerebral calcification was localized in the basal ganglia, dentate nuclei, vermis superior, and cerebral white matter (Fig. 2, Table 2).

Sural nerve and soleus muscle biopsies. The light and electron microscopical examinations of the sural nerve, including teased fiber studies and histometry, revealed slight signs of axonal neuropathy. The soleus muscle biopsy showed no marked abonormalities; but some intrafascicular fat cells and a single angular atrophic muscle fiber were observed.

Case 2

Case 2, the father of case 1, was examined at age 51 years, just after the diagnosis of IHPT had been made in his son. At that time, studies of serum Ca, P, Mg, PTH, and calcitonin revealed no abnormalities. He had normal health until age 56, when he was admitted to the Department of Internal Medicine after suffering a generalized seizure. Chvostek and Trousseau signs were positive. There was hypocalcemia (Ca: 1.60 mmol/l) and hyperphosphatemia (P: 1.39 mmol/l). PTH was undetectable. Intravenous-

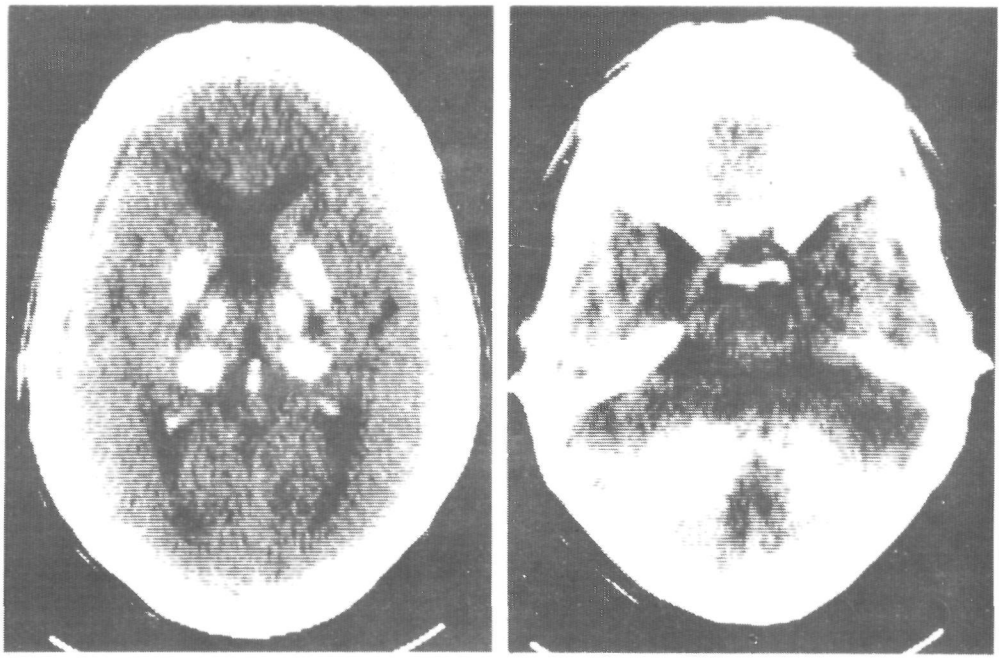


Fig. 3. CT scan of case 2 showing calcification in the dentate nuclei and basal ganglia.

ly administered parathyroid hormone provoked a normal decline of Tm/GFR. Serum concentrations of Mg and liver enzymes were normal, as were the results of the other laboratory tests performed as in case 1. Radiological examination of hands, long bones, and skull did not reveal any abnormality.

The diagnosis of IHPT was made and treatment with dihydrotachysterol was started. Subsequently, the Ca concentration returned to a normal level and seizures were no longer observed.

At age 59 years he was examined at the Department of Neurology. A general physical examination revealed no abnormalities. Chvostek and Trousseau signs were negative. Neurological examination revealed slight cogwheel rigidity and a masklike face. His gait wat ataxic and there was a slight dysmetria. These striocerebellar symptoms were less pronounced than those found in his son (case 1). Sensation was normal. Plantar reflexes were flexor. Ophthalmolgical examination revealed no abnormality.

Table 1. Latencies of somatosensory evoked potentials (SSEP) in idiopathic hypoparathyroidism (IHPT)

Case[a]	Sex	Age (yrs)	Duration of clinical manifestation (yrs)	Latencies (ms)				
				Specific complex		Nonspecific complex		
				N20	P45	P100	N145	P200
1	M	25	9	21.6	44.8	116[c]	160[c]	280[c]
2	M	59	3	21.5	45.0	146[c]	258[c]	350[c]
A	M	40	20	21.0	42.0	268[c]	380[c]	[b,c]
B	M	58	10	25.6[c]	54.0[c]	106	236[c]	[b,c]
C	F	27	9	22.4	36.0	152[c]	200[c]	[b,c]
Normal values. Mean				19.2	41.2	96.5	126	203
SD				2.4	4.5	8.0	15.0	17.0

[a] Cases 1 and 2 represent two patients described in the current paper. Cases A, B, and C are three other patients with IHPT (sporadic form)
[b] Peak could not be detected (latency > 500 ms)
[c] Latencies > mean + 2 SD

Psychological examination. GIT IQ: 103. The test profile was disharmonic (range 2.8 sigma). Estimated IQ according to school performance: 115. Trailmaking test: 7 points. Benton test: 2 items correct. These test results are consistent with mental deterioration.

The EEG revealed no abnormalities. Electromyograms and conduction velocities of motor and sensory nerves were normal. There were no signs of latent tetany within 3 min of hypoxemia. SSEP studies showed an abnormal nonspecific complex (Table 1).

Skull radiograms showed calcification in the basal ganglia and dentate nuclei (Fig. 3, Table 2).

Case 3

Case 3, a sister of case 1, was investigated at age 15 years, when the diagnosis of IHPT was made in her brother. Serum Ca, P, Mg, PTH, and calcitonin levels were normal. She had a normal history until age 23, when she was admitted to the Department of Internal Medicine after

Table 2. Localization of the intracerebral calcification in three cases with autosomal dominant idiopathic hypoparathyroidism (IHPT)

Case	Duration of IHPT (yrs)	Calcification in		
		Basal ganglia	Dentate nuclei	Cerebral white matter
1	11	+	+	+
2	3	+	+	–
3	0	–	–	–

suffering a generalized seizure. Except for positive Chvostek and Trousseau signs, the results of general physical, neurological and ophthalmological examinations were normal. Biochemical investigations revealed hypocalcemia (Ca: 1.80 mmol/l) and hyperphosphatemia (P: 1.60 mmol/l).

Serum PTH was undetectable. Intravenously administered PTH provoked a normal decline of Tm/GFR. Results of the other laboratory tests performed as in case 1 were normal.

The diagnosis of IHPT was made and treatment with dihydrotachysterol was started. Subsequently, the Ca concentration returned to a normal level and seizures were no longer observed.

Psychological and clinical neurophysiological examinations were not performed. Radiograms of skull, hands and long bones, as well as CT scan, revealed no abnormalities.

DISCUSSION

The clinical and biochemical studies in these cases are consistent with IHPT. The pedigree (Fig. 1) strongly suggests autosomal dominant inheritance. However, the disorder could be inherited as an autosomal recessive if the father (case 2) is homozygous and his wife heterozygous. Because of the chance of this combination is very remote in such a rare disorder, the autosomal dominant mode of inheritance is far more likely.

Reviewing the literature, we found 23 cases (13 males, 10 females) in

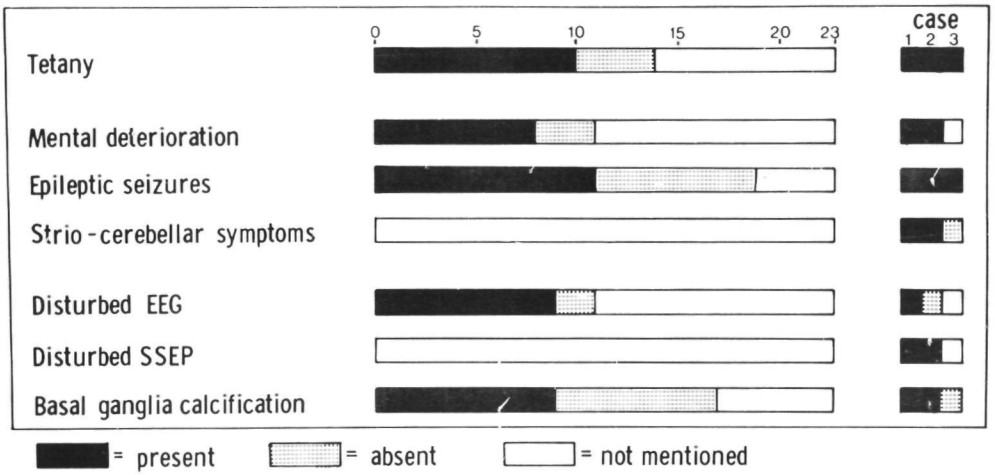


Fig. 4 Neurological symptoms in 23 previously published cases and our 3 presented cases with autosomal dominant idiopathic hypoparathyroidism

5 families where autosomal dominant IHPT is described [1, 5, 20, 27]. The neurological symptoms mentioned are described in Fig. 4. In many cases the first clinical manifestation of IHPT was epilepsy, which was controlled when normocalcemia was achieved. This illustrates that in patients with seizures of unknown etiology, hypocalcemia has to be considered.

Cases 2 and 3, having shown normal serum Ca and P levels, subsequently developed hypoparathyroidism a few years later. As fas as we know, such an occurrence has been reported only once in a case of familial idiopathic hypoparathyroidism [6].

Hypomagnesemia may be associated with hypoparathyroidism [28, 40]. However, the hypomagnesemia found in case 1 was probably due to alcohol abuse. In our opinion, the elevated SGOT, SGPT, and gamma GT concentrations, the axonal neuropathy and the abnormal findings in the muscle biopsy were also a consequence of alcohol abuse.

Detailed neuropathological studies of familial IHPT have not yet been reported. However, some sporadic cases have shown deposits of calcium and phosphate in and around the capillary walls of the basal ganglia, dentate nuclei, cortical layers, and in the cerebral and cerebellar white matter [8, 21]. In vivo, this intracerebral calcification can be diagnosed by plain

skull radiograms. The incidence in IHPT is not known. In 50 cases of IHPT or surgically induced hypoparathyroidism, calcification in the basal ganglia detected by plain skull radiograms was found in 28% [4]. Because the CT scan is much more sensitive in detecting intracerebral calcification than plain skull radiograms [29], the incidence may prove to be higher. Until now, detailed CT scan studies have been reported in only three sporadic cases of IHPT. In two cases calcification was observed in the basal ganglia and in the cerebral white matter [22, 42]; in the third case the dentate nuclei were also involved [9].

Calcification in the basal ganglia only has been related to many disorders caused by exogenous or endogenous (familial or nonfamilial) factors [23, 41]. Calcification in the striopallidodentate system has, however, only been reported in cases of hypoparathyroidism [9, 23], idiopathic striopallidodentate calcinosis [3, 23, 35], and Cockayne's syndrome [34, 39]. The lack of correlation between the relatively minor clinical symptomatology and the extent of the basal ganglia calcification, which we have found in our investigations, has been observed frequently in cases where the basal ganglia calcification was detected by CT scan [19, 41]. This could be explained by the results of neuropathological studies, showing that in the calcified areas the nerve cells remain intact for a long time [8, 26].

In cases 1 and 2, the skull radiograms showed an increase in intracerebral calcification. Varying the kilovoltages used for skull radiography also varies the extent of the revealed calcification. This could therefore be the cause of the increase. However, in the cases described above the quality of the skull radiograms did not vary significantly. The increase in intracerebral calcification, observed while serum calcium was normal owing to dihydrotachysterol therapy, suggests that there are more factors influencing the calcifying process than merely hypocalcemia. This theory is also supported by the presence of normocalcemia in idiopathic striopallidodentate calcinosis [3, 23, 35] and in Cockayne's syndrome [18, 34]. Table 2 suggests an increase in intracerebral calcification with the duration of IHPT. However, like many other autosomal dominant inherited disorders, IHPT may have a variable expression, which could also explain the difference in extent. The observation that the dentate nuclei calcification

in case 1 was less pronounced than those in case 2 (Figs. 2 and 3) indicates that still more factors influence the calcifying process.

The SSEP studies conducted in cases 1 and 2 (Table 1) show a normal specific complex, which reflects the spinothalamocortical projection, indicating a normal function of the white matter. The nonspecific complex, which is a reflection on the diffuse spread of sensory information over the cortex, was abnormal. This indicates dysfunction of the cortical gray matter [7, 13].

Because SSEP studies in IHPT have not yet been reported, we studied consecutively three patients with sporadic IHPT (Table 1). They showed mental deterioration, striocerebellar symptoms and calcification in the striopallidodentate system. In one of them (case B, Table 1) polyneuropathy was also present. The delayed latencies of the specific complex of the SSEP (Table 1) probably are a consequence of this. In all cases with IHPT the SSEP studies indicated gray matter dysfunction. This finding correlates positively with the psychological test results, which showed mental deterioration.

The results of our studies indicate that IHPT is also manifested by dysfunction of the cerebral cortical layers, basal ganglia and dentate nuclei. It is still unknown whether tetany is a consequence of peripheral or central nervous system disorder [12].

Further studies are required in order to assess the relative importance of epilepsy, mental deterioration, striocerebellar symptoms, intracerebral calcifications, and SSEP disturbances in the evaluation of familial and sporadic cases of IHPT.

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PROGRESSIVE IDIOPATHIC STRIO-PALLIDO-DENTATE CALCINOSIS (FAHR'S DISEASE) WITH AUTOSOMAL RECESSIVE INHERITANCE

Report of Three Siblings

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B. ter Haar, J. Prick

Eur. Neurol. (1982) 22: 58-64

3 siblings with symmetrical calcifications in the strio-pallido-dentate system are described. Parathyroid function was normal and there were no signs of central or peripheral myelinopathy. This is the 9th family reported with autosomal recessive idiopathic strio-pallido-dentate calcinosis and the first to be investigated by computerized tomography (CT). CT scans appeared to be superior to plain skull radiograms to assess the localization and the extent of the calcification in vivo. The calcifications were the least extensive in the youngest and the most extensive in the eldest. It is suggested that the calcifying process is a progressive disorder. It seems to start in the dentate nuclei and pons, and subsequently extends to the basal ganglia and to the radiation of the corpus callosum.

INTRODUCTION

Symmetrical calcifications in the strio-pallido-dentate system have been referred to as Fahr's disease, cerebral calcinosis and strio-pallido-dentate calcinosis (SPDC) [12]. Most patients with SPDC show progressive mental deterioration, and pyramidal, extrapyramidal and cerebellar signs [12]. Familial SPDC has been described with either an autosomal dominant or an autosomal recessive mode of inheritance [4, 12]. The autosomal dominant inherited disorder is reported to be associated with hypoparathyroidism and pseudohypoparathyroidism [12]. However, 6 families with autosomal dominant SPDC without endocrinologic or somatic abnormalities have been described [4]. The autosomal recessive inherited disorder is associated with Cockayne's syndrome, which is characterized by somatic abnormalities (dwarfism, senile appearance, hypersensitive dermatitis, retinitis pigmentosa) as well as by neurologic disturbances (progressive SPDC, central and peripheral myelinopathy) [21]. 8 families with autosomal recessive SPDC without endocrinologic or somatic abnormalities have been recorded [1, 6-8, 13, 14, 16, 22]. In all reported cases, the diagnosis was made by plain skull radiograms; in some cases it was also confirmed by neuropathologic studies [1, 3, 6, 14].

Using computerized tomography (CT), it is possible to locate and estimate the volume of the intracerebral calcifications more exactly than with plain skull radiograms [10].

We report here the results of clinical, neuroradiologic and electroneurophysiologic investigations in 3 siblings with SPDC and describe the findings of nerve and muscle biopsies in 1 sibling.

CASE REPORT

The genealogic tree of the non-consanguineous family (fig. 1) suggests an autosomal recessive mode of inheritance.

Case 1

This 41-year-old ex-nurse was seen in our department because of progres-

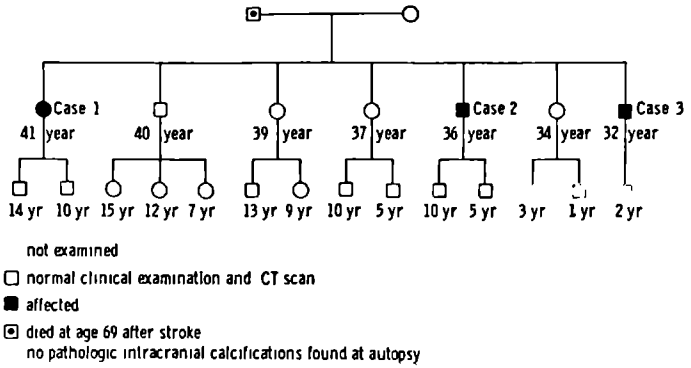

Fig.1. The pedigree of the cases with strio-pallido-dentate calcinosis. Figures below box or circle represent ages of the subjects in years.

sive impairment in speech and motor ability, which had originated about 4 years before. Appearance, height and the results of medical examination were normal. There were no deformities of hands, feet, skin or nails. Enamel and tooth development were normal.

Neurologic examination revealed choreic movements of head, tongue and limbs. There was a moderate dysarthria. The gait was ataxic and there was a slight dysmetria. The myotatic reflexes were normal, while plantar reflexes were flexor. Sensitivity was normal. The ophthalmologic examination showed no disturbances.

Psychological examination: general intelligence WAIS full scale IQ: 95 (verbal IQ: 107; performance IQ: 82). Wechsler memory scale: MQ: 96. About 18 months later WAIS full scale IQ was 87 (verbal IQ: 97; performance IQ: 76). Trail-making test: 2 points on A and B (cut off point: 12). Benton test: 3 items correct (expected score: 8 items). These test results strongly suggest mental deterioration.

Laboratory tests, including hematologic evaluation, hepatic, renal, adrenal, thyroid and pituitary function tests and electrophoretic analysis of serum proteins were normal. Appropriate studies excluded mercury and lead intoxications, deficiencies of thiamine, pyridoxine, cobalamine, folate and ascorbate,and tuberculosis, toxoplasmosis or syphilis. Other tests giving normal results included those for serum lipids, amino acids in plasma and urine, plasma shortchain fatty acids and organic acids, lysosomal

enzymes, ceruloplasmine, lactate, pyruvate and oral glucose tolerance. Serum calcium, phosphorus, magnesium, zinc, calcitonin, parathormone and 24-hour urinary calcium, phosphorus and magnesium excretion were normal. Intravenous injection of 200 USP units parathormone (Eli Lilly) gave a normal increase of urinary phosphorus and 3′:5′-AMP excretion. Cerebrospinal fluid studies included those for cell count, protein content, protein and immunoelectrophoresis, chloride, sodium, potassium, calcium, phosphorus, magnesium, zinc, copper, glucose, lactate, pyruvate, aspartate transaminase, lactate dehydrogenase and creatine phosphokinase; the results of these studies were normal. Cerebrospinal fluid amino acids (including glutamic acid, glycine and γ-aminobutyric acid), homovanillic acid and 5-hydroxyindole acetic acid were also normal.

Audiograms, electrocardiogram, karyogram and radiograms of hands, feet and long bones were normal.

Case 2 and 3

Case 2, a 36-year-old male, and case 3, a 32-year-old male, had normal histories. General and neurologic examination were normal. Results from the same laboratory tests as performed in case 1 showed no abnormalities.

INVESTIGATION OF THE NERVOUS SYSTEM

Central Nervous System

Neuroradiology. In case 1, radiograms of the skull showed dense symmetrical calcifications in the area of the basal ganglia and dentate nuclei. The CT scan of case 1 revealed extensive symmetrical calcifications in the striatum, globus pallidus, dentate nucleus, pons and in the radiation of the corpus callosum. In cases 2 and 3, the radiograms of the skull were normal. However, the CT scans revealed that in case 2 there were extensive symmetrical calcifications in the dentate nuclei and moderate symmetrical calcifications in all other areas mentioned in case 1. In case 3, the calcifications, visible on the CT scans, were restricted to the dentate nucleus and pons (fig. 2).

Electroencephalography and Evoked Potentials.
The electroencephalograms of the 3 siblings were similar: brain stem dysfunction was indicated with a projection in both temporal regions. Somatosensitive, visual and brain stem auditory evoked potentials were normal.

Peripheral Nervous System
Electroneurographic Measurements. Electromyograms and conduction velocities of motor and sensory nerves were normal in the 3 siblings.

Sural Nerve and Soleus Muscle Biopsies. In case 1, light- and electron-microscopic examinations, including teased fiber studies and histometry, revealed no abnormalities in particular, no signs of segmental de- and remyelination were observed.

DISCUSSION

The eldest sibling suffered from a progressive disorder manifested by mental deterioration, strio-cerebellar symptoms and calcifications in the strio-pallido-dentate system pons and radiation of the corpus callosum. In the 2 younger siblings the calcifications were less extensive, and, at the time of this study, no neurological disturbances were detected. Metabolic disorders, especially parathyroid dysfunction, have been excluded in all 3 cases. There were no signs of the somatic abnormalities and the peripheral and central myelinopathy associated with Cockayne's syndrome [21].
Reviewing the literature, we found 25 cases of autosomal recessive idiopathic SPDC in 8 families (table 1). The age at onset of symptoms was recorded in 23 cases: in 9 cases from 3 families [1, 8, 14] the symptoms appeared before age 10, in 12 cases from 4 other families [6, 13, 16, 22] the symptoms became manifest at middle age (fig. 3). This suggests there is an infantile and an adult form of the disorder.
Detailed neuropathologic studies on some of the cases [3, 6, 14] revealed extensive symmetrical pericapillary calcifications in the putamen, caudate nucleus, globus pallidus, dentate nucleus, brain stem and in the cerebral

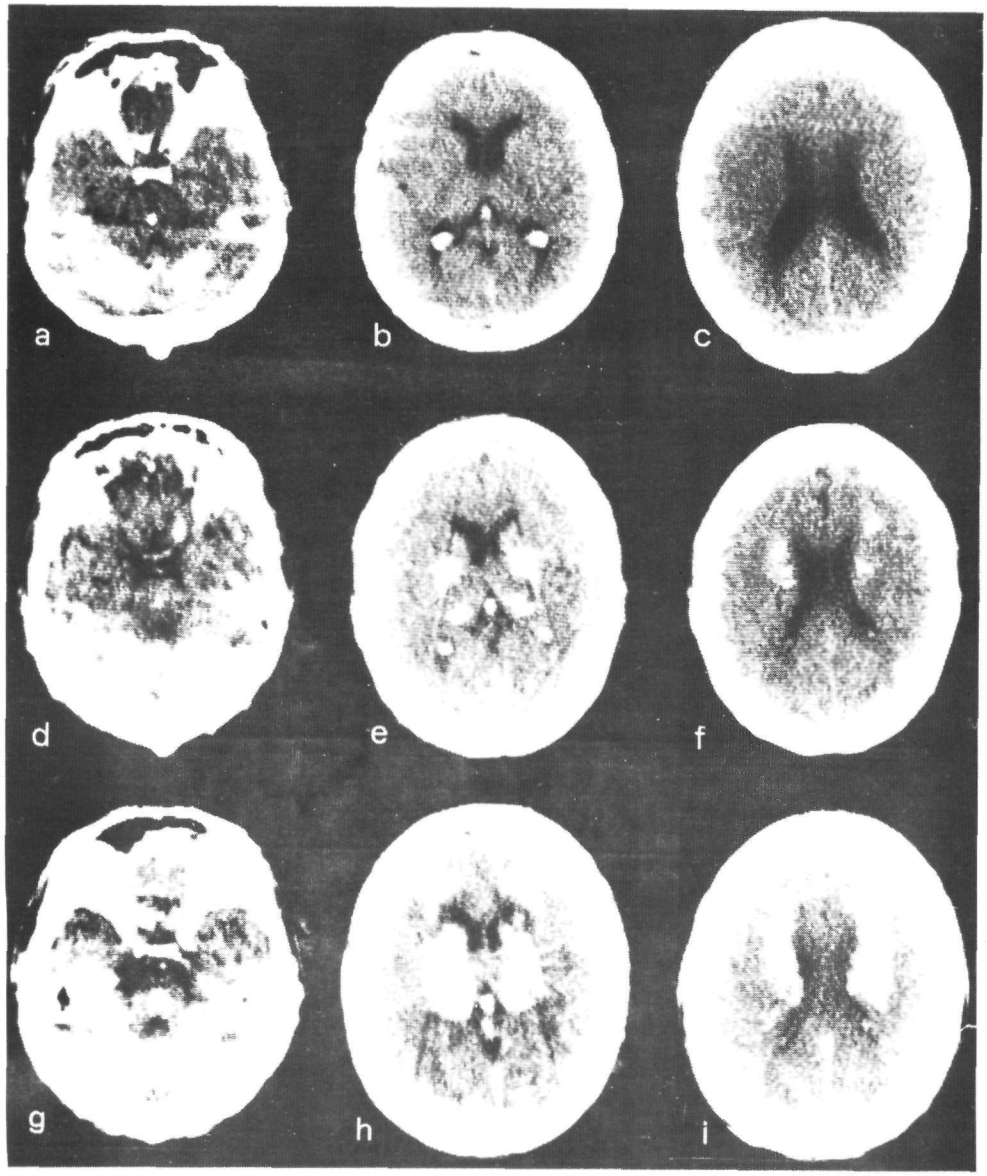

Fig. 2. CT scan of 3 siblings with autosomal recessive idiopathic striopallido-dentate calcinosis. With increasing age, more symmetrical calcifications are visible in the striatum, globus pallidus, dentate nucleus, pons and radiation of the corpus callosorum. a-c Case 3 (age 32 years). d-f Case 2 (age 36 years). g-i Case 1 (age 41 years).

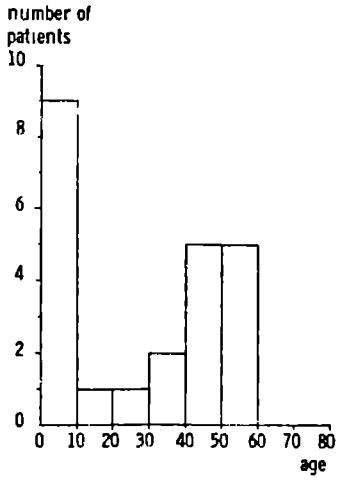

Fig. 3. Age at onset of symptoms in 23 patients with autosomal recessive idiopathic strio-pallido-dentate calcinosis.

and cerebellar white matter. The origin of the calcifications is not known. *Matthews* [13] and *Nyland and Skre* [16] found in their cases a subnormal phosphorus diuresis after exogenously administered parathormone, suggesting an unusual type of pseudohypoparathyroidism. We could not confirm these findings in the present study.

Although CT scans are much more sensitive than plain skull radiograms in detecting intracerebral calcifications [10], SPDC is rarely observed in vivo. In studies involving a total of 26,100 CT scans [5, 10, 15, 20], the occurence of symmetrical calcifications in the basal ganglia was determined. In 123 of these scans (0,5%), symmetrical calcifications in the basal ganglia were found and in 13 scans (0.05%) there were also symmetrical calcifications in the dentate nuclei. These reports did not give enough relevant clinical information to determinate the presence of endocrinologic or somatic disturbances. In addition to the above studies, there are reports of 5 sporadic cases of hypoparathyroidism with SPDC, visible on CT scan [2, 7, 18], and 5 sporadic cases of SPDC without endocrinologic or somatic disturbances [9, 11].

In the siblings investigated here, the increase in the calcifications with the age of the patients suggests a progressive calcifying process, which probably begins in the dentate nuclei and pons, and subsequently occurs in the basal ganglia and in the radiation of the corpus callosum.

Because (pseudo)hypoparathyroidism is the only known metabolic disorder

Table 1. Summary of findings in 8 previously published families and our presented family with autosomal recessive idiopathic strio-pallido-dentate calcinosis.

	Reference No								This study
	[8]	[22]	[13]	[14]	[6]	[1]	[7]	[16]	
Number of affected siblings	3	3	3	3	3	3	2	5	3
Mental deterioration	+	o	+	+	+	+	+	+	+
Psychosis and or depression	o	o	o	o	+	o	o	+	−
Dysarthria	+	+	+	+	+	o	−	+	+
Epileptic seizures	+	o	−	−	o	+	−	+	−
Pyramidal signs	+	+	−	+	+	o	+	+	−
Extrapyramidal signs	+	+	+	+	o	+	+	+	+
Ataxia	+	+	+	o	o	o	o	+	+
Disturbed EEG	o	−	o	o	+	+	+	+	+
Calcifications in basal ganglia	+	+	+	+	+	+	+	+	+
Calcifications in dentate nuclei	+	+	+	+	+	+	+	+	+
Calcifications in white matter	+	+	o	+	+	+	+	+	+
Central atrophy	o	o	o	o	+	+	o	+	−
Autopsy examination	+[1]	−	−	+	+	+	−	−	−
Miscellaneous		ψ	ω	ψ		ψ		ω	

+ = Present, − = absent, o = not reported, ψ = retinitis pigmentosa, ω = atypical pseudohypoparathyroidism.
[1] Reported by *Beirne* [3]

associated with SPDC, it has been suggested that idiopathic SPDC could be a consequence of a disorder in the parathormone-regulated calcium metabolism [13, 16, 19]. As autosomal recessive inheritance is usually associated with an enzyme deficiency, an enzyme deficiency somewhere in the parathormone regulated calcium metabolism may play an important role in the manifestation of idiopathic SPDC. Further investigations are necessary to confirm this theory.

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CHAPTER IV

PERIPHERAL AND CENTRAL MYELINOPATHY IN COCKAYNE'S SYNDROME. REPORT OF 3 SIBLINGS

M. Smits, F. Gabreels, W. Renier, E. Joosten, A. Gabreels-Festen, H. ter Laak, A. Pinckers, G. Hombergen, S. Notermans, H. Thijssen

Neuropediatrics (1982) 13: 161-167.

ABSTRACT

Three siblings with *Cockayne's* syndrome are reported. Sural nerve biopsies revealed segmental de- and remyelination with onion-bulb formation. Disturbed visual and brain-stem auditory evoked responses indicated demyelination of the central nervous system. The peripheral and central myelinopathy increased with age, suggesting a progressive disorder. Our observations support the theory of *Cockayne's* syndrome being a leukodystrophy.

INTRODUCTION

In 1936 *Cockayne* described 2 siblings who, after apparently normal early development, manifested dwarsfism, microcephaly, mental retardation, senile appearance, photosensitive dermatitis, retinal pigmentation, optic atrophy, cataract, prognathism and partial deafness. In 1946 he reported on the progressive character of the disease.About 90 cases have subsequently been noted and many new features have been included in *Cockayne's* syndrome (CS): disproportionately long extremities, carious teeth, thickened skull bones, calcifications of the basal ganglia, normal pressure hydrocephalus, peripheral neuropathy and extrapyramidal, pyramidal and cerebellar signs (*Guzzetta* 1972, *Jin* et al 1979, *Soffer* et al 1979). Almost none of the reported cases showed all these symptoms and laboratory investigations have not revealed any consistent abnormalities. The occurence of CS in siblings suggested autosomal recessive inheritance. The most constant neuropathologic findings have been white matter atrophy with patchy demyelination and calcifications of the basal ganglia (*Moossy* 1967, *Crome* and *Kanjilal* 1971, *Soffer* et al 1979).

We report here the results of clinical, electroneurographic and neuroradiologic investigations in 3 siblings with CS and describe the histopathologic findings in nerve and muscle biopsies.

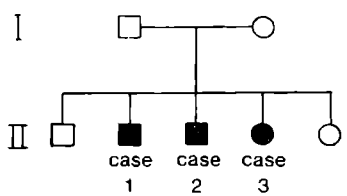

Fig. 1 The pedigree of the cases of Cockayne's syndrome

CASE REPORTS

Case 1

This 19-year-old male was investigated because of dwarsfism and a regression in psychomotor development. His parents are healthy and unrelated.

Except for his brother (case 2) and sister (case 3), there is no history of similarly affected children in the family.

With the exception of a photosensitive dermatitis, noted at the age of 6 months, his prenatal, natal and postnatal histories were unremarkable until age 3. From that time and increasing with age, dysarthria, tremors and a spastic-atactic syndrome developed. From age 10 a decrease in intelligence was noted. At age 12 routine laboratory investigations, electroencephalogram and skull radiograms were all normal, but by age 17 skull radiograms indicated calcifications in the area of the basal ganglia. From that age onwards he suffered relapsing psychotic periods, which could however be controlled with neuroleptic therapy.

At age 19 he was seen at our department. On physical examination, he was small and thin with an old looking "bird headed dwarf" appearance, prognathism, loss of facial subcutaneous fat and heavy eyebrow ridges. His teeth were very carious. His height was 135 cm (P2.5), his weight 33,4 kg (P2.5) and the head circumference was 51.5 cm (P5). Lungs and heart were normal. The liver was palpable two fingers below the costal margin. The spleen was not palpable. The genitals were normal. He had a marked kyphoscoliosis. There was a considerable dysarthria. A coarse postural tremor of both hands and head, always present, increased with intentional movement. Further neurologic examination revealed a bilateral spastic-atactic syndrome with atrophy and weakness of the distal muscles. The myotatic reflexes were low, while plantar reflexes were extensor. Sensibility was normal. Psychological evaluation revealed mental retardation (IQ 77). Dermatologic investigation confirmed that the skin was very sensitive to ultraviolet light. Visual acuity for both eyes was 0.8. There was a slight nuclear punctate cataract. The fundus aspect was normal. The audiograms showed considerable perceptive high tone losses (65 dB at 4000 Hz). Normal relevant laboratory tests included renal, adrenal, thyroid and pituitary function tests, calcium, phosphorus, calcitonin, parathormone, copper, ceruloplasmin, lysosomal enzymes, aminoacids in plasma and urine, chromosomal studies and electrocardiogram. Serum glutamic oxalate transferase (SGOT; N 5-15 U/l), serum glutamic pyruvate transaminase (SGPT; N 5-15 U/l) and γ glutamyl transpeptidase (γGT;

N 6-36 U/l) were slightly higher than normal: 40, 25 and 131 U/l respectively. The cerebrospinal fluid was normal except for an increased protein concentration (775 mg/l). Liver biopsy was normal.

Case 2

This 16-year-old male had the same history of intellectual deterioration dysarthria, photosensitive dermatitis, tremors and spastic-atactic syndrome as his affected brother. On physical examination, he had the same old looking appearance. His height was 137 cm (< P2.5), his weight 37 kg (< P2.5) and the head circumference was 52.5 cm (P25). Heart, lungs, abdomen and genitalia were normal. His skin was very sensitive to ultraviolet light. The dysarthria, tremors and spastic-atactic syndrome were less pronounced relative to those found in his elder brother. IQ was 74. Visual acuity for both eyes was 0.5. There was a slight nuclear punctate cataract. The fundus aspect was normal. The audiograms showed moderate perceptive high tone losses (40 dB at 4000 Hz). Laboratory test results were normal except for slightly elevated SGOT. SGPT and γ GT: 37, 131 and 48 U/l respectively.

Case 3

This 13-year-old female also had a history of tremors, dysarthria, intellectual deterioration and spastic-atactic syndrome. Upon physical examination, she had the same old looking face but no loss of subcutaneous fat. Her height was 129 cm (<P2.5), her weight 30.5 kg (P5) and the head circumference was 50.5 cm (P10). Heart, lungs and abdomen were normal. Her skin was very sensitive to ultraviolet light. Compared with her affected brothers, the temors and spastic-atactic syndrome were the least pronounced. IQ was 75. Visual acuity for both eyes was 0.7. There was a slight nuclear punctate cataract. The fundus aspect was normal. The audiograms were within normality. Results from laboratory investigations were normal except for slightly elevated SGOT, SGPT and γ GT: 33, 90 and 40 U/l respectively.

Neuroradiology

In case 1, radiograms showed that calcifications increased between ages 17 and 19. In case 2 and 3, skull radiograms were normal. Computed tomography (CT) scanning showed symmetrical calcifications in the basal ganglia and dentate nuclei in all 3 siblings. This occurred most extensively in case 1 and least extensively in case 3. The ventricles were enlarged. The ventriculocranial index (*Hahn* and *Rim* 1976) was 0.46 in case 1, 0.44 in case 2, and 0.37 in case 3 (normal value ± SD: 0.31 ± 0.04).

Electroneurophysiology

The electroencephalograms of the 3 siblings were not essentially different, showing a little slowing of basal activity.

Brainstem auditory evoked response (BAER)

The results of brainstem evoked response audiometry are summarized in Table 1. In case 1, peak I and III could not be detected. Except for the I-III interpeak latency in case 3, all latencies were delayed significantly ($P < 0.05$), being the most pronounced in the eldest, and the least pronounced in the youngest patient.

Table 1 Interpeak latencies in brainstem auditory evoked responses in 3 siblings with Cockayne's syndrome

Interpeak latency		I III					III V					O V				
Case	Age (yr)	Latency (ms)	Normal values Mean	SD	abs	%	Latency	Normal values Mean	SD	abs	%	Latency	Normal values Mean	SD	abs	%
1	19											6 94	5 21	0 16	1 73	33
2	16	2 43	2 03	0 16	0 40	20	2 88	1 76	0 19	1 12	64	6 67	5 21	0 16	1 46	28
3	13	1 98	1 93	0 14	0 05	3	2 52	1 65	0 19	0 90	56	5 77	4 94	0 83	0 83	17

^abs absolute difference between patient and normal values to be interpreted as absolute nerve conduction delay
^% abs expressed in percentage
0 stimulus onset
– not detectable
Normal values according to *Debruyne* et al (1980)

Neuro-ophthalmologic examination

Visual evoked cortical potentials (VECP) were recorded in the usual way. A flashed-pattern-evoked-response was present in cases 2 and 3, but absent in case 1. A pattern-reversal-evoked response was present in case 3, but absent in case 1 and 2.

Color vision was examined following the procedure described by *Pinckers* (1980). The results are listed in Table II. In case 1, the pseudo-isochromatic color (PIC) tests indicated a super-mild tot mild red-green defect. Red-green defects were present in the Panel D 8/2. The FM 100 Hue error score was high. There was a neutral zone at yellow, red and red-purple with the New Color Test Box 6/4 (NCT 6/4). In cases 2 and 3, the PIC, NTC 6/4 and Panel D 8/2 test results were normal. The FM 100 Hue error score progressively increased from case 3 to case 1.

Table II Color vision - as described by Pinckers (1980) - in 3 siblings with Cockayne's syndrome

			PIC tests			FM 100 Hue Derivatives			Anomaloscope Nagel Model II
Case	Age (yr)	Eye	TMC	AOH-R-R	*Ishihara* (error score)	NCT 6/4	Panel D 8/2	FM 100 Hue (error score)	(*Rayleigh* equation)
1	19	RE	screening defect	screening RG-defect	6	1//T+	1//P 1//PD 1//DT	282	not performable
		LE	screening defect	mild screening RG-defect	5	neutral zone YR RP	2//P 2//T	261	1 00
2	16	RE	N	-	0	3//T+	2 ME	241	1 06
		LE	N	-	0	1//T	1//DT 1//T+	172	1 06
3	13	RE	N	-	2	N	MET	189	0 96
		LE	N	-	2	N	1//P 1//T+	169	1 00

codification according to *François* and *Verriest* (1957) N normal - not examined

INVESTIGATIONS OF THE PERIPHERAL NERVOUS SYSTEM

Electroneurographic measurements

The nerve conduction volocities were decreased: the eldest patient showed the most pronounced decrease, the youngest patient the least (Table III).

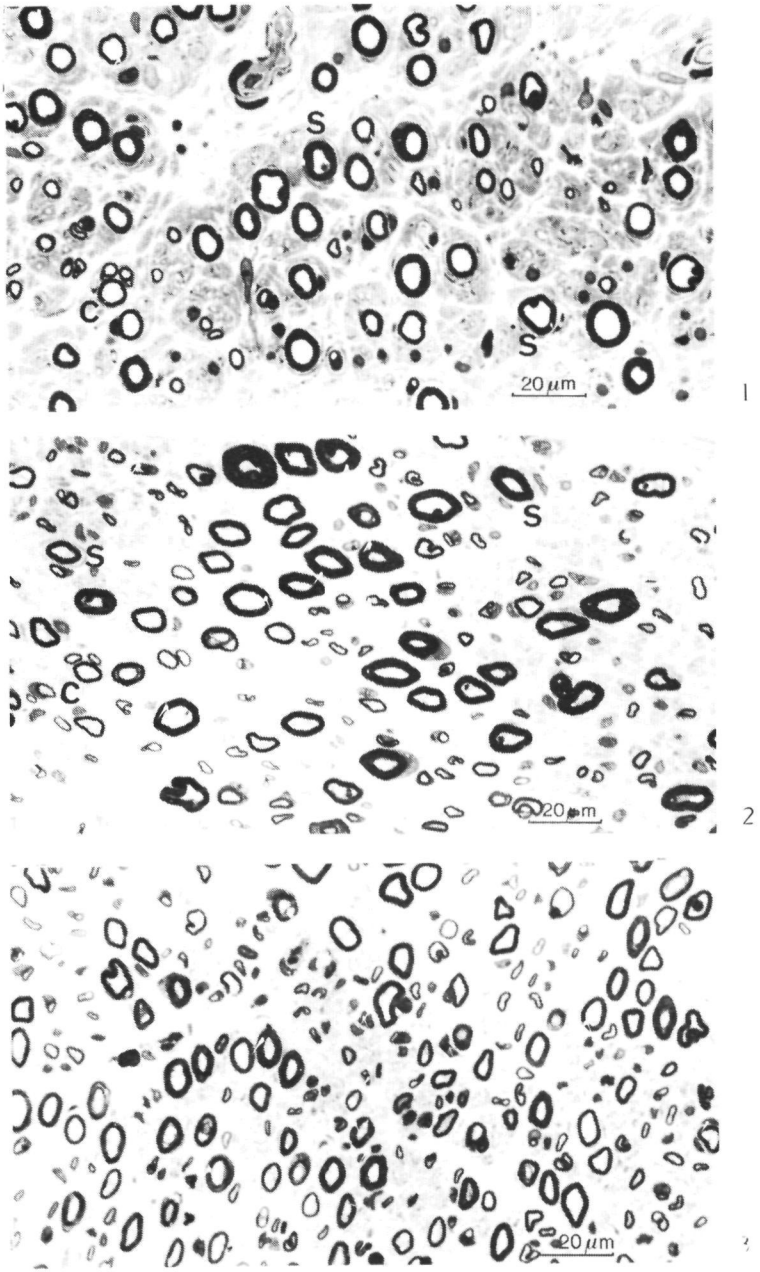

Fig. 2 Sural nerve biopsies. The density of myelinated fibers is diminished in case 1 and 2. Slight onion-bulb formation (S) is evident in case 1, and is also slightly apparent in case 2. Few clusters of small fibers (C) are seen in case 1 and 2. In case 3 there is an obvious lack of large diameter in fibers. Epon 1 μm 850 x

Sural nerve biopsies

The sural nerve of case 1 showed the most extensive abnormalities. The density of myelinated fibers was moderately diminished, as was the total number of myelinated fibers (Figs. 2 and Table IV). The relative incidence of large fibers (more than 10 μm) was diminished compared with age matched controls (Fig. 3). There was evidence of chronic segmental and paranodal demyelination and remyelination (Table IV) with onion-bulb formation (Figs. 2 and 4). Secondary myelin breakdown (axonal degeneration) was observed sporadically. There were only a few clusters of small meylinated fibers, indicating regeneration after axonal degeneration. Deposits of calcium could not be demonstated.

In case 2, the density of mylinated fibers was low-normal. A normal total number of myelinated fibers was encountered (Table IV). Signs of segmental and paranodal de- and remyelination with slight onion-bulb formation were present but were less pronounced than in case 1. Axonal degeneration was rarely observed and clusters were not seen.

In case 3, the density and total number of myelinated fibers were normal (Table IV). The relative incidence of large fibers (more than 10 μm) was somewhat diminished (Fig. 3). The teased fiber preparations showed some segmental de- and remyelination. Onion-bulbs, however, were not observed. There was no axonal degeneration, nor cluster formation.

Muscle biopsies

The biopsy of the soleus muscle of case 1 indicated the presence of severe abnormalities. Both, fascicles consisting of normal sized type I fibers

Table III Electroneurographic examination in 3 siblings with Cockayne's syndrome

	Case 1 (19 yr)	Case 2 (16 yr)	Case 3 (13 yr)	Normal values Mean	SD
Motor nerve conduction velocities (m/s)					
lateral popliteal nerve		31	32	50	7.5
tibial posterior nerve	30	31	38	48	4.0
median nerve	34	39	40	57	5.6
Sensory nerve conduction velocity (m/s)					
sural nerve	31	39	44	45	3.4

– no response obtainable from denervated extensor digitorum brevis muscle

Table IV Density of myelinated fibers and condition of teased myelinated fibers in the sural nerve of 3 siblings with Cockayne's syndrome

Case	Age (yr)	Density (No/mm²)	TTFA (mm²)	Type of myelinated fibers (%)* A	C	D	E	F	Total (%) CDF
1	19	5500	1 3	43	27	6	0	24	57
2	16	7100	1 1	71	5	2	2	20	27
3	13	9200	0 8	80	0	3	0	17	20

Density mean controls + SD (n = 14 age 11–30 yr) 10350 3200
TTFA (total transverse fascicular area) mean controls 0 85 mm² range 0 4 – 1 3
* Capitals refer to condition of the teased fibers (criteria according to *Stevens* et al 1973)
A = normal appearance C = paranodal demyelination D = segmental demyelination E = axonal degeneration with linear rows of myelin balls F = paranodal or segmental remyelination

and fascicles with atrophic fibers surrounded by many fat cells, could be seen. Many muscle fibers in the biopsy consisted of packed nuclei surrounded by the sarcolemma. In some fascicles about half of fibers showed a target or targetoid-like appearance The terminal innervation ratio (TIR), measured according to *Coërs* et al (1973), was greatly increased: 5.6 (N < 1.1), indicating a severe loss of motor axons. This loss was compensated by the sprouting of the remaining axons.

The biopsy of the soleus muscle of case 2 showed less marked disturbances, with only some atrophic and hypertrophic fibers. The checkerboard-pattern of type I and type II fibers was disturbed. The TIR was slightly increased (1.3).

The biopsy of the soleus muscle of case 3 showed normal sized muscle fibers, although the checkerboard-pattern was slightly disturbed.

DISCUSSION

Reviewing the literature concerning *Cockayne*'s syndrome, we found 96 cases in 66 families: 42 females, 53 males and one individual where the sex was not mentioned (references 1-3, 5-9, 11-14, 18-20, 22-28, 30-38, 40, 42-50, 52-55). In these cases many different symptoms were reported (Fig. 5). In addition to progressive deterioration after normal development in the first year and autosomal recessive inheritance, most authors include the following features as the main symptoms of CS: mental retardation,

senile appearance, photosensitive dermatitis, dwarfism, central motor disturbances, intracerebral calcifications, retinal pigmentation and peripheral neuropathy. In only 51% of the described cases were 6 or more of the main symptoms mentioned. The conclusion that there is a unique cluster of diagnostic criteria, minimal and necessary for the diagnosis of CS, cannot be made.

Detailed neuropathologic studies, as reported by *Moossy* (1967), *Rowlatt* (1969), *Crome* and *Kanjilal* (1971), *Sugarman* et al (1977) and *Soffer* et al (1979), revealed central white matter atrophy with patchy demyelination and preservation of axons. These authors also found extensive extravascular calcifications located in the basal ganglia, dentate nuclei, white matter and throughout the cortex. In vivo calcifications of the basal ganglia, visible on skull radiograms, were reported in 25 cases (references 1, 3, 7, 18, 22, 26, 32, 35, 36, 42, 49). On CT scanning they were visible in 3 cases (*Brumback* et al 1978, *Jin* et al 1979). As far as we know, cerebellar calcifications have until now not been detected on CT scanning in CS. Calcifications of the basal ganglia have also been reported in parathyroid dysfunction and cerebral anoxia (*Löwenthal* and *Bruyn* 1968). In reviewing the literature, *Boller* et al (1977) found 9 families with idiopathic familial basal ganglia calcifications, and added one more family to this list.

Peripheral nerve conduction velocities were normal in 3 cases (*Ohno* and *Hirooka* 1966, *Sugarman* et al 1977) and slowed in 15 cases (references 1, 3, 7, 19, 22, 32, 44, 47). In 7 cases nerve biopsies had been performed, showing chronic demyelinating neuropathy in 3 cases (*Moosa and Dubowitz* 1970, *Roy* et al 1973). Normal findings were described by *Gamstorp* (1972), *See* et al (1974), and *Jin* et al (1979).

In our cases, all the main symptoms of CS were present, except for microcephaly and retinal pigmentation. The results of VECP and color vision examinations may be interpreted as symptoms of the desynchronisation of the conductive system, pointing to optic neuropathy. There were no signs of compressing optic neuropathy, so these findings may be due to a genuine demyelinating process of the optic conductive system. The VECP alterations and color vision disturbances (e.g. FM 100 Hue error score) increased with age, suggesting a progressive disease.

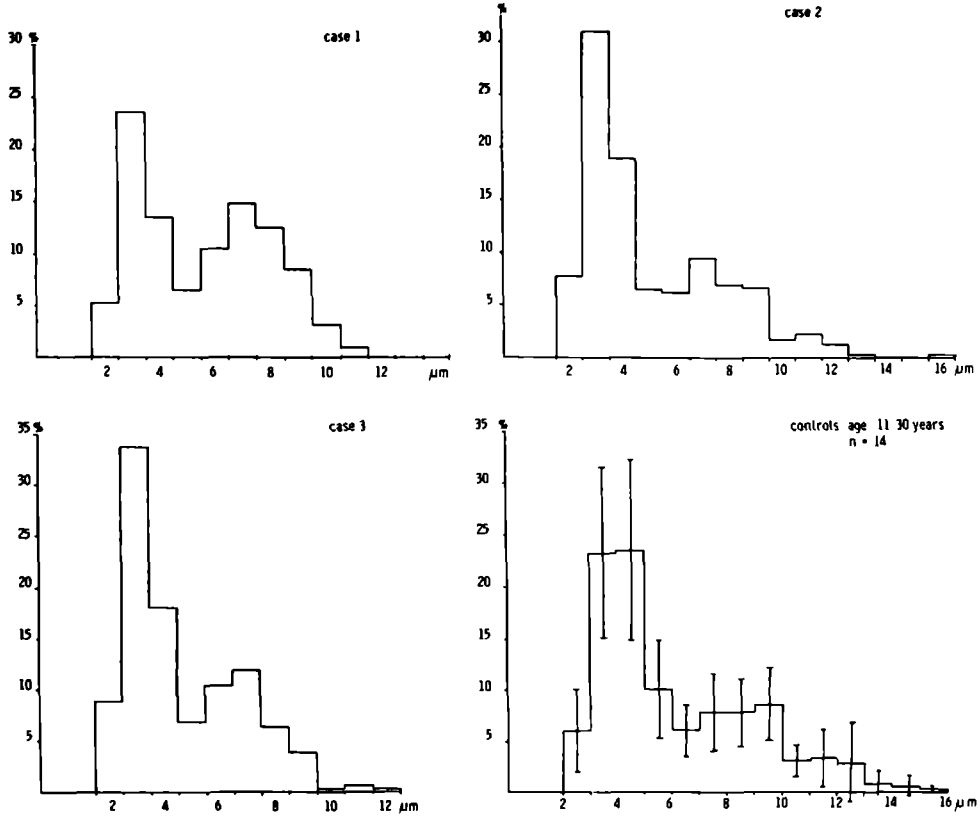

Fig. 3 Sural nerve fiber diameter spectra in 3 siblings with Cockayne's syndrome and controls

The audiograms showed perceptive high tone losses, also increasing with age. When audiometric losses are caused by middle ear lesions or when high tone losses are caused by cochlear lesions, a shift of the whole nerve pattern in the BAER may occur due to a slowing of the 0-I latency (representing action potentials from the acoustic nerve). However, slowing of the interpeak latencies represent brainstem nerve conduction delay and thus retrocochlear lesions. In our study, we clearly observed increased interpeak latencies, which lead us to the conclusion that the perceptive high tone losses are at least of retrocochlear origin. Not only the high tone losses, but also the interpeak latencies increased with age, suggesting a progressive retrocochlear disease of the auditory pathway.

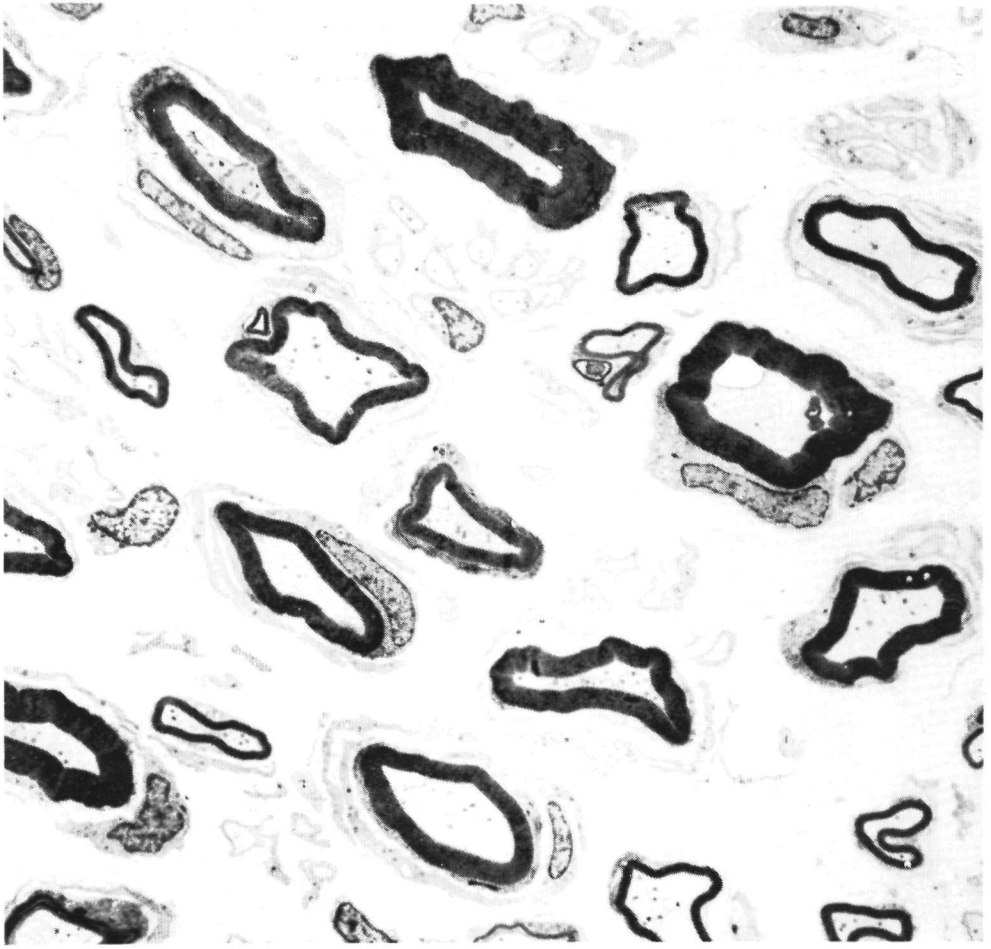

Fig. 4 This electron-micrograph shows that almost all myelinated fibers are surrounded by one or more layers of Schwann cell processes which form so-called onion-bulbs. Several thinly myelinated fibers are seen, indicating remyelination. The unmyelinated fibers don't show any abnormalities. 1700 x

Some aspects of the peripheral demyelinating neuropathy also showed an increase with age. Onion-bulbs as non-specific signs of repeated de- and remyelination *Dyck* 1975) were most pronounced in the eldest patient and barely noticeable in the youngest. The same is true for the incidence of de- and remyelinated segments in teased fibers (Table IV), which was inversely correlated with the nerve conduction velocities. The decrease

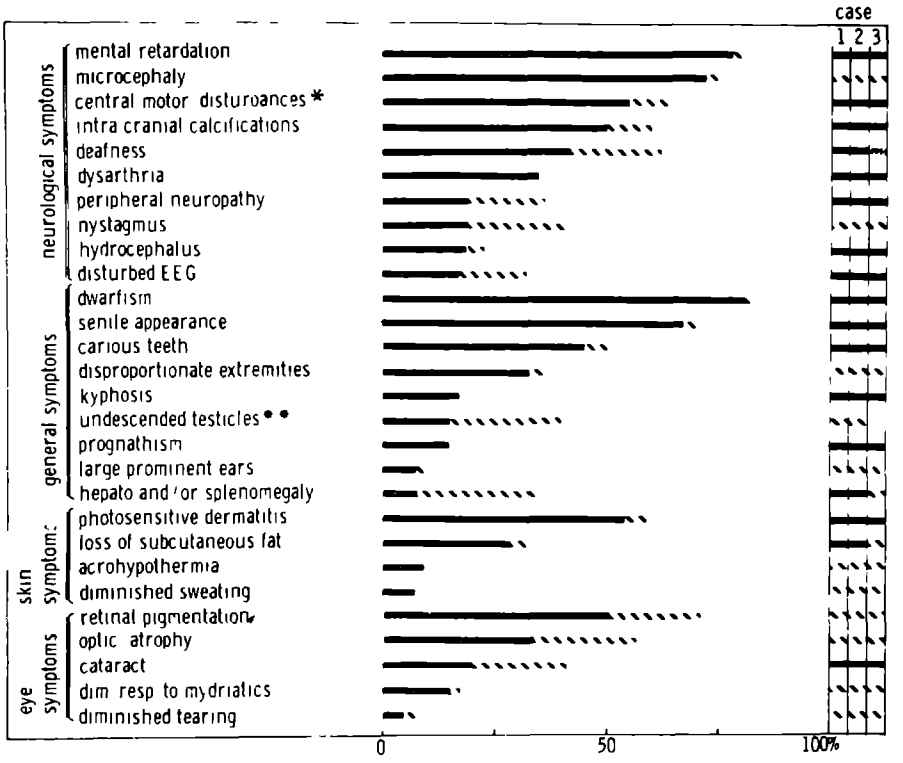

Fig. 5 Frequency of symptoms described in Cockayne's syndrome

present
not present
not mentioned
irrelevant

* pyramidal and/or extrapyramidal and/or cerebellar signs

** thickened skull bones and/or calcifications of the basal ganglia

*** 100% = 53 male cases (all other items 100% = 96 cases)

in myelinated fiber density and the reduction in diameters of the largest myelinated fibers were not evidently correlated with age (Fig. 3). The decrease in large diameter myelinated fibers, as seen in our cases, is a well known fact in other demyelinating neuropathies and is most probable an non-specific result of repeated de- and remyelination (*Raine* 1978). Type grouping, as seen in the muscle biopsies, is a consequence of axonal loss rather than the result of de- and remyelination. It is likely that axonal

loss is a secondary result, the primary being the de- and remyelinating process.

In our cases, the clinical, neuroradiologic, electroneurographic and histopathologic disturbances increased with age, suggesting a progressive disease. Demyelination of the peripheral nerve was proved by the nerve biopsy findings, while demyelination in the central nervous system was suggested by ophthalmologic and audiologic findings. The concurrence of demyelination of the peripheral and central nervous system points to a disturbance of myelin or myelinating cells, as seen in some leukodystrophies. Our observations strongly support the theory, as proposed by *Moosa* and *Dubowitz* (1970), of *Cockayne*'s syndrome being a leukodystrophy.

ACKNOWLEGDEMENTS

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PRESENCE OF CEREBRAL PARATHYOID HORMONE-RESPONSIVE ADENYLCYCLASE IN HUMANS

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F. Gabreëls

Ann. Neurol. (1983) 14: 348-349

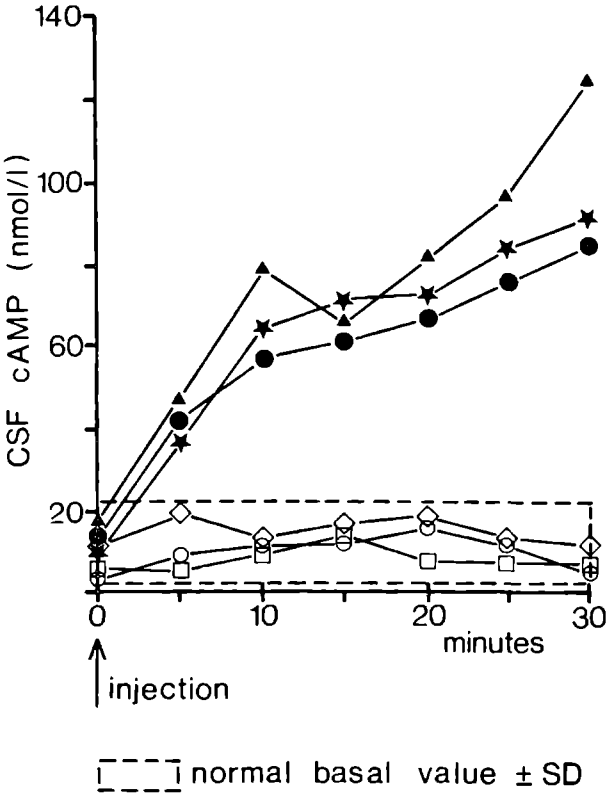
Adenylcyclase plays an important role in many extracerebral and cerebral metabolic pathways by activating the transformation of adenosine triphosphate into cyclic adenosine monophosphate (cAMP). This enzyme can be stimulated by a number of different hormones [1, 3, 4, 9].

The presence of renal parathyroid hormone (PTH)-responsive adenycyclase has been demonstrated by the administration of PTH; such administration resulted in increased urinary production of nephrogenous cAMP [5]. Demonstration of cerebral PTH-responsive adenycyclase, however, has not yet been described. In order to determine if a cerebral PTH-responsive adenylcyclase exists, the effect of PTH on cerebrospinal fluid (CSF) cAMP concentrations was studied.

One healthy 21-year-old man and two healthy women, 45 and 56 years old, remained at complete bedrest after an overnight fast prior to intravenous injection of 200 IU of bovine PTH (Hormon-Chemie, Munich). A different hormone batch was used for each person. Lumbar punctures were performed as described previously [2]. The needle remained in position for 30 minutes. Simultaneous blood and CSF samples were obtained prior to and every 5 minutes after PTH injection. Serum and CSF samples were frozen at -20°C immediatly after termination of the experiment. In the same way, CSF samples were collected in three other healthy adults prior to and after intravenous injection of saline. Measurement of cAMP was done by high-performance liquid chromatography [6]. Normal basal values for CSF cAMP were 13.4 $\pm$ 9.0 nmol/L (mean $\pm$ standard deviation) (n-17). Detection accuracy was 2 nmol/L.

The administration of PTH produced a five- to tenfold rise in plasma cAMP, which peaked 10 minutes after injection and then declined exponentially until 25 minutes after injection, when it reached the initial prestimulation serum cAMP level. Simultaneously, during the 30 minutes after injection, the CS cAMP concentrations increased significantly ($p < 0.003$; Spearman's rank correlation test for each subject), as is shown in the Figure. After the saline injection, the CSF cAMP concentrations remained within the normal basal range (see the Figure).

This last observation indicates that the PTH-induced four- to sevenfold increase in CSF cAMP concentration was not the consequence of a stress effect of the lumbar puncture and the systemic injection. Changes in



Concentration-time curves of cyclic adenosine monophosphate in cerebrospinal fluid after injection of parathyroid hormone (filled symbols) or saline (open symbols)

CSF cAMP concentrations brought about by pharmacological agents reflect alterations in the cerebral cAMP metabolism [2]. Thus, the observed PTH-induced increase in CSF cAMP concentrations reflects the increase in cerebral cAMP. Because cerebral cAMP formation is the direct consequence of stimulation of cerebral adenylcyclase [3], our observation suggests the presence of cerebral PTH-responsive adenylcyclase.

Hypofunction of this cerebral adenylcyclase might play a role in the cerebral dysfunction associated with hypoparathyroidism [7].

It is not likely that the intact PTH molecule, which is a single chain polypeptide of eighty-four amino acids [8], is able to cross the blood-brain barrier. It is possible, however, that some biologically active fragments [8] could cross this barrier and reach their cerebral target organs.

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CALCIUM-PHOSPHATE METABOLISM IN AUTOSOMAL RECESSIVE IDIOPATHIC STRIO-PALLIDO-DENTATE CALCINOSIS AND COCKAYNE'S SYNDROME

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SUMMARY

In three siblings with autosomal recessive idiopathic strio-pallido-dentate calcinosis (SPDC) and in three other siblings with Cockayne's syndrome (CS) studies on plasma values of calcium and phosphate, intestinal calcium absorption, radiograms of the hands and studies on the influence of parathyroid hormone (PTH) on the renal threshold for phosphate revealed no abnormalities. In one of the SPDC patients and one of the CS patients the effect of PTH on the cyclic adenosine monophosphate (cAMP) concentrations in urine and cerebrospinal fluid (CSF) were determined. In both a normal response of urinary cAMP was noted. In the CS patient the response of CSF cAMP was also normal. The SPDC patient, however, had a significantly decreased response of CSF cAMP.

It is suggested that a decreased sensitivity of the cerebral anenylate cyclase complex is involved in the etiology of autosomal recessive idiopathic SPDC Subsequently this order could be considered as cerebral pseudohypoparathyroidism. The etiology of CS remains unknown.

INTRODUCTION

Autosomal recessive idiopathic strio-pallido-dentate calcinosis (SPDC) is characterized by calcification in the strio-pallido-dentate system, extrapyramidal and cerebellar signs and mental deterioration (*Löwenthal* and *Bruyn* ; 1968). Results of extensive biochemical investigations of patients with idiopathic SPDC are usually within the normal range (*Löwenthal* and *Bruyn* , 1968; *Smits* et al., 1983a).

Autosomal recessive Cockayne's syndrome (CS) is characterized by the same symptoms as autosomal recessive idiopathic SPDC and, in addition, by dwarfism, senile appearance, microcephaly, signs of central and peripheral myelinopathy, photosensitive dermatitis, retinitis pigmentosa and many other somatic abnormalities (*Soffer* et al, 1979; *Smits* et al., 1982a).

Hypoparathyroidism may be associated with the neuroradiological and clinical signs of autosomal recessive idiopathic SPDC and, in addition, may be associated with epilepsy and tetany *Frame*, 1976; *Smits* et al., 1982b).

Biochemically, hypoparathyroidism is characterized by hypocalcemia and hyperphosphatemia due to either a deficient secretion of parathyroid hormone (PTH) (primary or surgical hypoparathyroidism) or unresponsiveness of the receptor to PTH (pseudohypoparathyroidism).

Because (pseudo)hypoparathyroidism is the only known metabolic disorder associated with calcification in the strio-pallido-dentate system, it has been suggested that idiopathic SPDC and CS are the consequence of a disorder in the PTH-regulated calcium-phosphate (Ca-P) metabolism (*Nyland* et al., 1977; *Smits* et al., 1982a). In three siblings with autosomal recessive idiopathic SPDC and in three other siblings with CS we tested this hypothesis.

MATERIAL AND METHODS

Patients

Three siblings with autosomal recessive idiopathic SPDC (S_1, S_2 and S_3), reported in detail in an earlier study (*Smits* et al., 1983a), showed calcifications in the strio-pallido-dentate system (Fig. 1). At the time of our

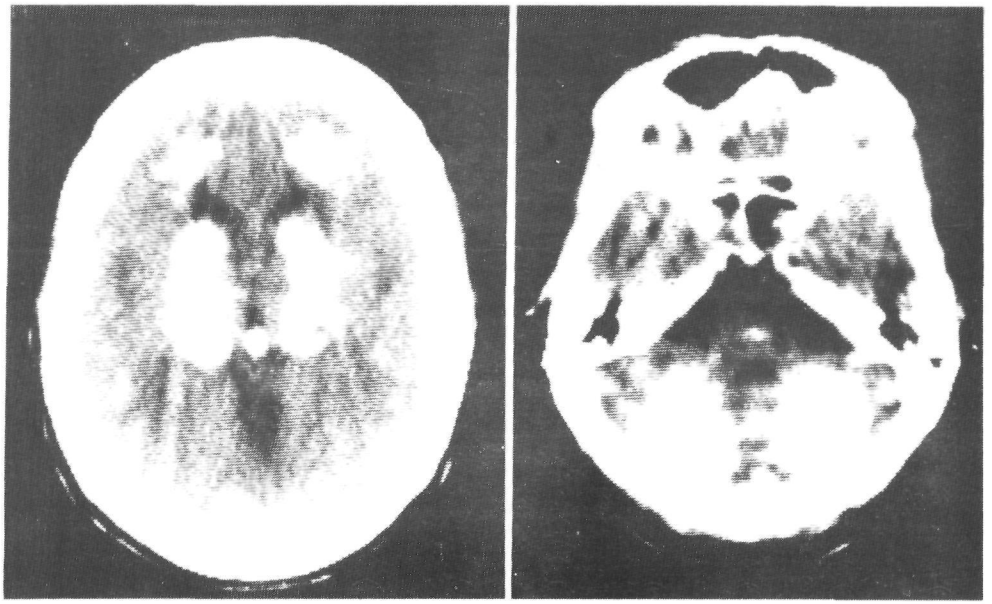

Fig. 2 CT scans of patient S_1 showing calcification in the basal ganglia and dentate nuclei

investigations only the eldest showed additional neurological signs, i.e. mental deterioration and progressive extrapyramidal and cerebellar signs (Table 1). The results of extensive biochemical tests on blood, urine and cerebrospinal fluid (CSF) were normal. Radiograms of the hands showed no abnormalities.

Three other siblings with CS (C_1, C_2 and C_3), reported in detail in an earlier study (*Smits* et al., 1982a), showed calcifications in the strio-pallido-dentate system (Fig. 2), mental deterioration, pyramidal, extrapyramidal and cerebellar signs, polyneuropathy (Table 1), dwarfism, senile appearance and photosensitive dermatitis. Disturbed visual and brainstem auditory evoked potentials indicated demyelination of the central nervous system. Except for slightly elevated serum glutamic oxalate transferase, serum glutamic pyruvate transminase and γ-glutamyl transpeptidase concentrations, the results of extensive blood and urinary investigations were normal. In patient C_1 CSF was normal except for an increased protein concentration (775 mg/l). In patients C_2 and C_3 CSF was not investigated.

Table 1 Neurological findings in three siblings with autosomal recessive idiopathic strio-pallido-dentate calcinosis (S_1, S_2 and S_3) and three siblings with Cockayne's syndrome (C_1, C_2 and C_3)

Patient	S_1	S_2	S_3	C_1	C_2	C_3
Sex	F	M	M	M	M	F
Age (yrs)	41	38	33	19	16	13
Mental deterioration	+	–	–	+	+	+
Pyramidal signs	–	–	–	+	+	+
Extrapyramidal and cerebellar signs	+	–	–	+	+	+
Strio-pallido-dentate calcinosis	+	+	+	+	+	+
Demyelination in CNS* and PNS**	–	–	–	+	+	+

F = female, M = male, + = present, – = absent
* central nervous system, ** peripheral nervous system

Radiograms of the hands showed no abnormalities.

In these six patients Ca-P metabolism was studied.

Methods

Plasma, urinary and CSF Ca concentrations were measured with the cresolphtalein complexone reation (*Moorehead* and *Biggs*, 1974) and P with the

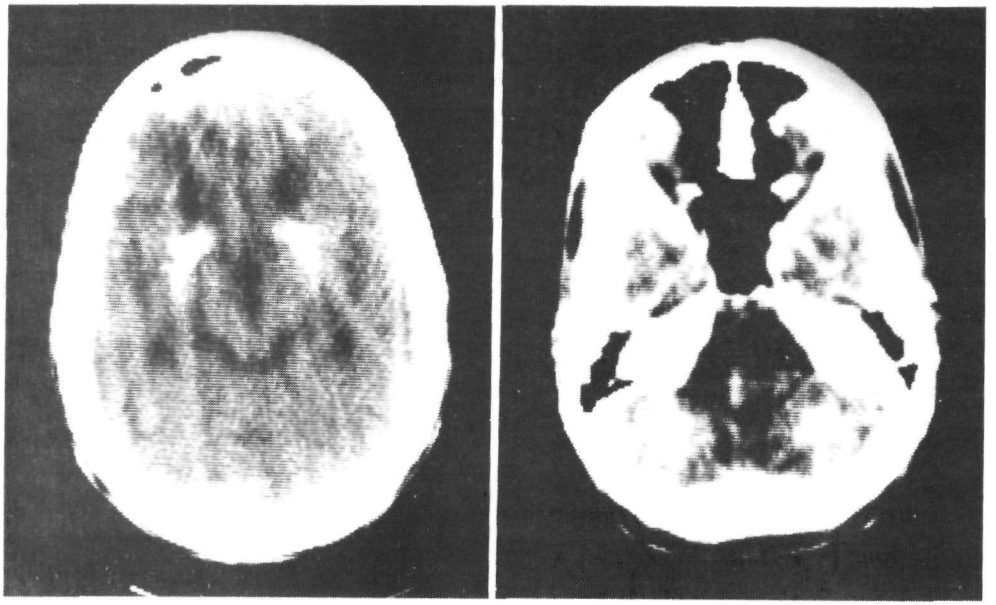

Fig. 2 CT scans of patient C_1 showing calcification in the basal ganglia and dentate nuclei

continuous-flow ultraviolet spectrophotometer (*Amador* and *Urban*, 1972). Plasma and urinary creatinine with the Jaffe reaction (*Henry* et al., 1974) and magnesium (Mg) with the Perkin-Elmer atomic absorption spectrophotometer 400. Plasma PTH and calcitonine concentrations were measured by a modified radioimmunoassay method, conducted by Dr. Hakking, Bergweg Hospital, Rotterdam, The Netherlands. Plasma 25 (OH) cholecalciferol and 1,25 $(OH)_2$cholecalciferol determinations by the high performance liquid chromatographic (HPLC) method of *Eisman* (1976) and CSF cAMP by the HPLC method of *de Abreu* et al., (1982).

PTH stimulation tests were conducted as follows: 200 UI bovine PTH (Hormon-Chemie Munich) was injected intravenously in the patients following an overnight fast. In all patients the same hormone batch was used. Blood and urinary samples were collected one hour before, just before and one, two and three hours after hormone injection for determination of the renal threshold for P (TmP/GFR, see *Bijvoet* et al., 1969) and cAMP. To correct for errors due to variation in the water content of urine, urinary concentrations of P and cAMP were expressed as mmol/mol creatinine respectively as µ mol/mol creatinine. In patients S_1 and C_1 some minutes before the PTH injection a lumbar puncture was performed in the lateral decubitus position with a 20-gauge needle that remained in position for 30 minutes. CSF samples were obtained immediately prior to and every 5 minutes after PTH administeration (*Smits* et al., 1983b). Immediately after termination of the PTH stimulation tests, serum, urine and CSF samples were stored at -20°C for 3 to 4 weeks prior to cAMP assay. Intestinal Ca retention was measured by a modification of the method described by *Sjöberg* et al. (1970). Following a single dose of 10µCi ^{47}Ca, given with 200 ml milk as carrier, the percentage absorption of this dose was determined by monitoring the retention of the isotope over a 3-week period, using a whole body counter.

RESULTS

The results of biochemical investigations on serum, urine and CSF are shown in Table 2 and the results of the PTH stimulation tests are given in Table 3. All results were within the normal range.

Tabel 2 Serum, urine and cerebrospinal fluid (CSF) values of various parameters involved in calcium-phosphate (Ca-P) metabolism and intestinal Ca retention studies in three siblings with autosomal recessive idiopathic strio-pallido-dentate calcinosis (S_1, S_2 and S_3) and in three siblings with Cockayne's syndrome (C_1, C_2 and C_3)

Patient		S_1	S_2	S_3	C_1	C_2	C_3	normal values
Serum	Ca (mmol/l)	2.21	2.37	2.53	2.60	2.58	2.60	2.20-2.60
	P (mmol/l)	0.83	0.88	1.09	1.09	1.22	1.19	0.76-1.24
	Mg (mmol/l)	0.81	0.79	0.81	0.81	0.83	0.85	0.80-1.00
	PTH* (pmol P_2/l)	0.10	0.09	0.08				< 0.20
	PTH** (pmol P_2/l)				4.0	3.4	4.0	2.0-12.0
	Calcitonine (µg HCT/l)	0.06	0.12	0.21	0.02	0.02	0.02	< 0.13
	25 (OH) cholecalciferol (ng/ml)	49	26	20	15	14	20	10-50
	1.25 $(OH)_2$ cholecalciferol (ng/100 ml)	5.6	3.4	4.1	4.8	5.3	6.0	2.0-6.0
Urine	Ca (mmol/24 h)	5.3	6.1	5.6	4.3	6.5	7.0	< 7.5
	Mg (mmol/24 h)	1.1	1.5	1.5	1.4	1.6	1.2	> 1.0
CSF	Ca (mmol/l)	1.08			1.18			1.02-1.22
	Mg (mmol/l)	0.49			0.50			0.37-0.50
Intestinal Ca retention (% dose)		26.7		28.2	17.2	27.3	26.9	14.5-30.0

* bovine parathyroid hormone (PTH) equivalent

** human parathyroid hormone (PTH) equivalent

Table 3 Results of parathyroid hormone (PTH) stimulation tests performed in one sibling with autosomal recessive idiopathic strio-pallido-dentate calcinosis (S_1) and three siblings with Cockayne's syndrome (C_1, C_2 and C_3) before (-) and after (+) intravenous injection of 200 IU PTH

Patient		S_1			C_1			C_2		C_3	
		P*	TmP/GFR	cAMP**	P	TmP/GFR	cAMP	P	TmP/GFR	P	TmP/GFR
Time (min)	60	1 30	0 80	0 41	2 14	1 13	2 0	1 25	1 63	0 53	1 62
	− 5	1 45	0 81	0 40	1 71	1 25	2 1	1 47	1 60	0 58	1 60
	+ 60	2 37	0 64	42 30	3 50	1 11	50 0	1 52	1 53	2 16	1 25
	+ 120	2 25	1 16	3 43	4 66	1 06	4 0	3 48	1 19	2 83	1 32
	+ 180	1 20	1 21	0 43	4 66	1 03	3 3	2 68	1 38	2 88	1 34

* mmol P/mmol creatinine

** µmol cAMP/mmol creatinine

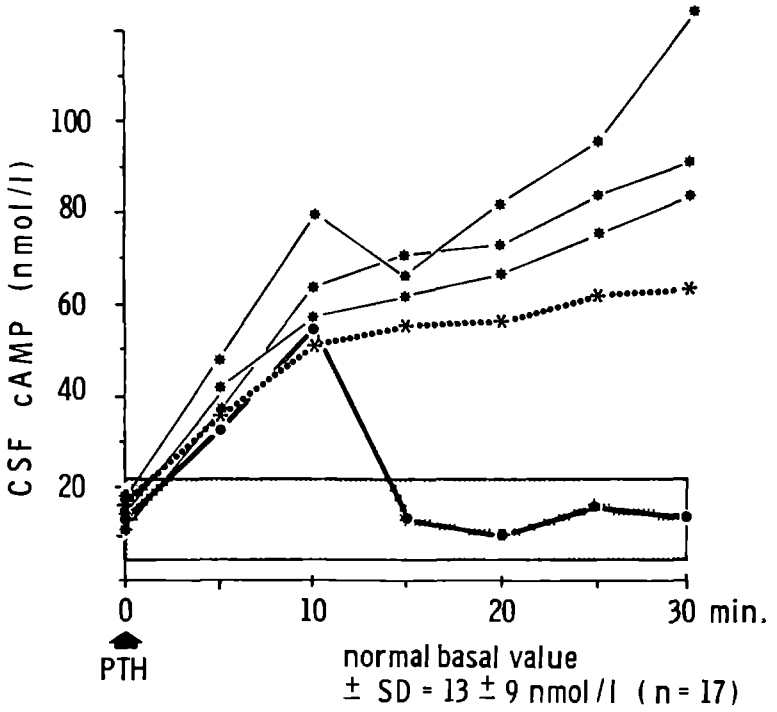

Fig. 3 Cerebrospinal fluid (CSF) cAMP concentrations in three healthy adults (*·····*), in patient C_1 with Cockayne's syndrome (•——•) and in patient S_1 with autosomal recessive idiopathic strio-pallido-dentate calcinosis (•——•) after intravenous injection of 200 IU parathyroid hormone (PTH). The data for the healthy adults have been described previously (Smits et al., 1983b)

The effect of PTH on CSF cAMP concentrations, examined in patients S_1 and C_1 and in three healthy adults (see *Smits* et al., 1983b), is shown in Fig. 3. According to Dixon's test (*Dixon*, 1950, 1951, 1953) the values observed in patient S_1 are significant outliers ($p < 0.05$) for t = 20 minutes. For t = 25 minutes the value is nearly significant ($0.05 < p < 0.10$).

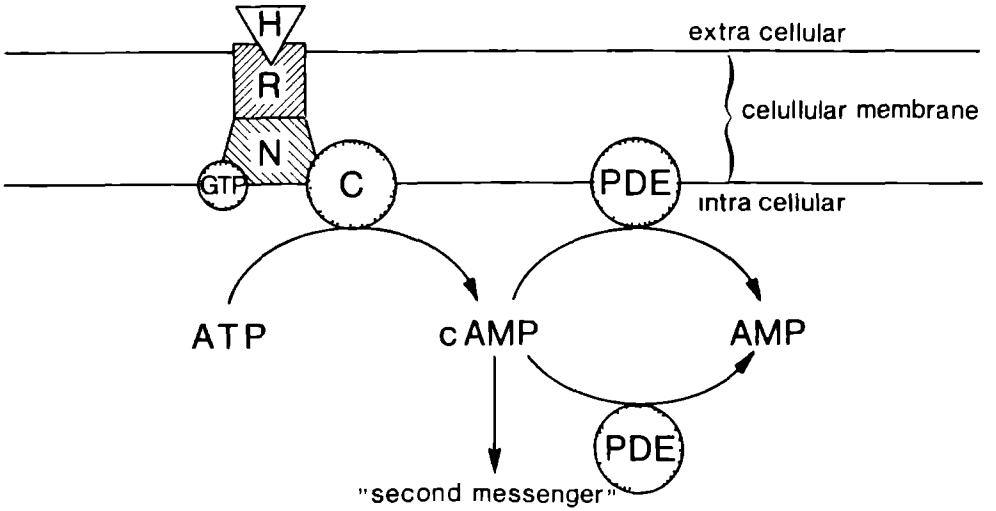

Fig. 4 Schematic representation of the adenylate cyclase complex (RNC) and phosphodiesterase (PDE) which regulate intracellular levels of cAMP. The hormone (H) binds to the receptor (R) which than attaches to the GTP-nucleotide regulatory unit (N) and activates the catalytic component (C) of the adenylate cyclase complex to produce cAMP. PDE can be membrane-bound or in the cytosol (adapted from Rodbell, 1980)

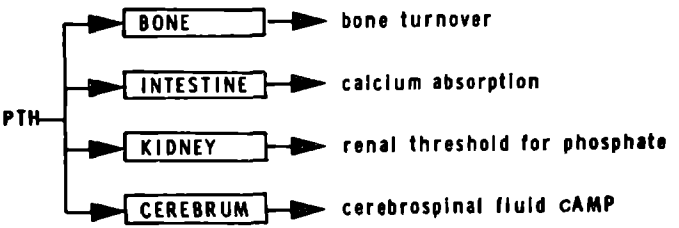

Fig. 5 Target organs and actions of parathyroid hormone (PTH)

Ca-P metabolism is regulated and influenced by many hormones and minerals. PTH plays a central role in this mechanism. In the target tissue for this hormone it stimulates the adenylate cyclase complex, which catalyzes the conversion of adenosine triphosphate (ATP) into cAMP, a second messenger, which in turn activates specific biochemical pathways in the cell (*Sutherland* , 1972). Phosphodiesterase catalyzes the conversion of cAMP into adenosine monophosphate (AMP) (Fig. 4). In addition to stimulation of the PTH-responsive adenylate cyclase complex, PTH may also regulate the Ca-P metabolism by other, largely unknown, mechanisms. The influence of PTH on Ca-P metabolism (Fig. 5) can be summarized as follows:

a) PTH stimulates the hydroxylation of 25 (OH) cholecalciferol into 1,25 $(OH)_2$ cholecalciferol, which stimulates the intestinal Ca absorption. The intestinal Ca absorption can be studied by measuring the intestinal retention of ^{47}Ca (*Sjöberg* et al., 1970).
b) PTH stimulates the adenylate cyclase complex located in the bone cells and plays an important role in bone turn-over. Subperiostal erosions, visible on radiograms, are indicative for hypoparathyroidism.
c) PTH stimulates the adenylate cyclase complex located in the renal proximal tubular cells. Stimulation results in an increase of urinary cAMP concentrations and a decrease in TmP/GFR (*Bijvoet* et al., 1969).
d) We have observed in three healthy adults that intravenously injected PTH resulted in an immediate rise in the CSF cAMP concentrations (Fig. 3). As there is a definite blood-brain barrier for cAMP (*Brooks* et al., 1977), it can be concluded that there exists a cerebral enzyme which stimulates the production of cerebral cAMP, i.e. a cerebral PTH-responsive adenylate cyclase (*Smits* et al., 1983b).

The last observation, that of a cerebral adenylate cyclase sensitive to extracerebrally administered PTH, raises intriguing questions concerning the mechanism of this stimulation. PTH might act at sites in the brain where there is no blood-brain barrier for PTH. Alternatively, there could be specific transport mechanisms for PTH uptake by the brain, or extracerebrally produced bioactive fragments of PTH might gain access to

the brain. Finally, the possibility must be considered that PTH might stimulate the production of extracerebral blood-born factors that can cross the blood-brain barrier to stimulate the cerebral adenylate cyclase complex. Further investigations are required to test these various possibilities.

In the present study the influence on extracerebral Ca-P metabolism was normal in all our cases, as judged by the results of the investigations on plasma values of Ca and P, intestinal Ca absorption, radiograms of the hands and studies on the influence of PTH on TmP/GFR. Moreover, in patients S_1 and C_1 PTH produced a normal response of urinary cAMP, consistent with a normal renal adenylate cyclase complex.

The study on the effect of PTH on CSF cAMP levels showed a normal response in the CS sibling C_1 , but a significantly decreased response in the SPDC sibling S_1 15 minutes after hormone administration (Fig. 3.). This decreased response could be due to leakage of CSF cAMP into the blood or by increased phosphodiesterase activity (see Fig. 4). However, the normal pre-stimulation CSF cAMP level indicates the existence of a normal blood-brain barrier. We would like to suggest that the decreased CSF cAMP levels in the SPDC patient could be due to a defect in the cerebral PTH-responsive adenylate cyclase complex. This defect could involve any component in the complex, including the receptor for PTH or the nucleotide regulatory unit (see Fig. 4). Like in pseudohypoparathyroidism the (PTH-responsive) adenylate cyclase complex in kidney and bone is defective (*Aurbach* , 1971), the defective cerebral PTH-responsive adenylate cyclase complex could be considered 'cerebral pseudohypoparathyroidism'.

As autosomal recessive inheritance is usually associated with a gene defect, expressed as an enzyme deficiency, autosomal recessive idiopathic SPDC could be the consequence of a gene defect, through which a defect in the cerebral adenylate cyclase complex is produced.

The etiology of CS remains unknown.

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ADDENDUM

Recently we studied a 13-year-old boy with autosomal dominant idiopathic SPDC. PTH injection did not change CSF cAMP, obtained in the above described way. Urinary cAMP response was normal.

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CHAPTER VII

CONCLUSIONS AND DISCUSSION

7.1 Introduction

Many different descriptions have been proposed on the symptomatology and etiology of strio-pallido-dentate calcinosis (SPDC) since its first mention by Virchov in 1856 (16).

Skull radiographical studies of patients with SPDC have revealed that this very rare neuroradiological condition is often associated with a specific entity of neurological signs, specifically those that are extrapyramidal and cerebellar. These studies have also shown that SPDC is often associated with a disturbed calcium-phosphate (Ca-P) metabolism (especially hypoparathyroidism) (1, 10, 12).

On the other hand, studies of SPDC by the much more sensitive CT-scan have revealed conflicting results: the frequency of SPDC diagnosed on CT-scan appeared to be much higher (0,5-1,6 %) than previously observed (3, 8, 13, 17); most SPDC patients diagnosed by the CT-scan did not show extra-pyramidal and/or cerebellar signs (8, 13, 17). These CT-scan studies also showed that SPDC can be associated with many exogenous and endogenous (familial and non-familial) factors (8, 17). The results of these studies convinced some researchers (9, 17) that SPDC, which is detected by chance by CT-scan, has no clinical significance, such as calcification in the pineal gland and choroid plexus, which also have no clinical significance.

In the last two decades new clinical neurophysiological and neuro-morphological methods have increased understanding of the functioning and anatomy of the central and peripheral nervous system, while new endocrinological methods have increased the knowledge of Ca-P metabolism. This leads naturally to the question of whether these same new methods could increase our knowledge of SPDC. In order to obtain a rather homogenous group of SPDC patients and to make it possible to leave exogenous factors out of consideration we restricted our studies on the symptomatology and etiology of SPDC to familial disorders with calcifications in both basal ganglia and dentate nuclei.

Table 1 Extent of SPDC, represented as +, ++ and +++ in the two patients with autosomal dominant idiopathic hypoparathyroidism (H1 and H2), the three patients with autosomal recessive idiopathic SPDC (S1, S2, S3) and the three patients with Cockayne's syndrome (C1, C2 and C3)

Patient	Extent of SPDC
H1	++
H2	++
S1	+++
S2	++
S3	+
C1	++
C2	++
C3	+

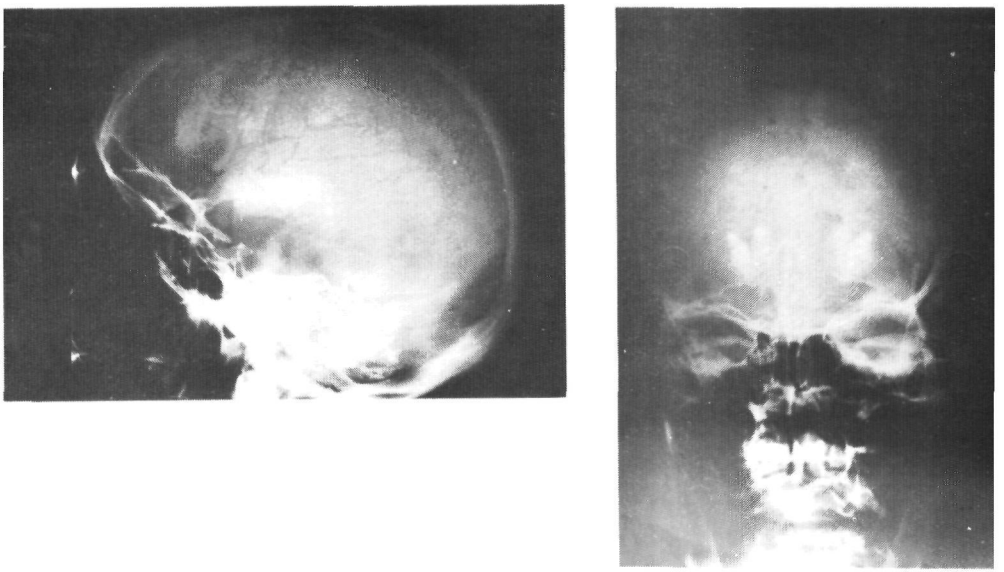

Fig. 1. Skull radiograms of the eldest patient with autosomal recessive idiopathic SPDC showing calcifications in the basal ganglia and dentate nuclei.

Studying a father, his son and his daughter, all three having autosomal dominant idiopathic SPDC; three siblings with autosomal recessive idiopathic SPDC and three siblings with Cockayne's syndrome, we intended to answer the following questions:

a. Is familial SPDC characterized by a specific entity of neurological signs?
b. Is a disturbance of the Ca-P metabolism involved in the origin of autosomal recessive idiopathic SPDC and Cockayne's syndrome?
c. Can indications be found for the presence of a cerebral parathyroid hormone (PTH)-responsive adenylcyclase complex?
d. Is the function of the cerebral PTH-responsive adenylcyclase complex disturbed in autosomal recessive idiopathic SPDC and Cockayne's syndrome?

7.2 Results of the studies on familial SPDC

7.2.1 Answers to the preceding questions

a. Is familial SPDC characterized by a specific entity of neurological signs?

The neurological signs of the investigated patients with familial SPDC described in chapter II, III and IV have been summarized in table 1 and figs. 1-4.

Each patient differed in the extent and location of the cerebral deposits (fig. 1, table 1) and in the nature of the clinical neurological, clinical neurophysiological and neuromorphological signs (fig. 2). There was no relation between age and extent of calcification (fig. 3). Also, the patients showing SPDC in similar intensities differed in the nature of the clinical neurological, clinical neurophysiological and neuromorphological signs (fig. 4).

These findings indicate that familial SPDC is not characterized by a specific entity of neuroradiological, clinical neurological, clinical neurophysiological and/or neuromorphological signs.

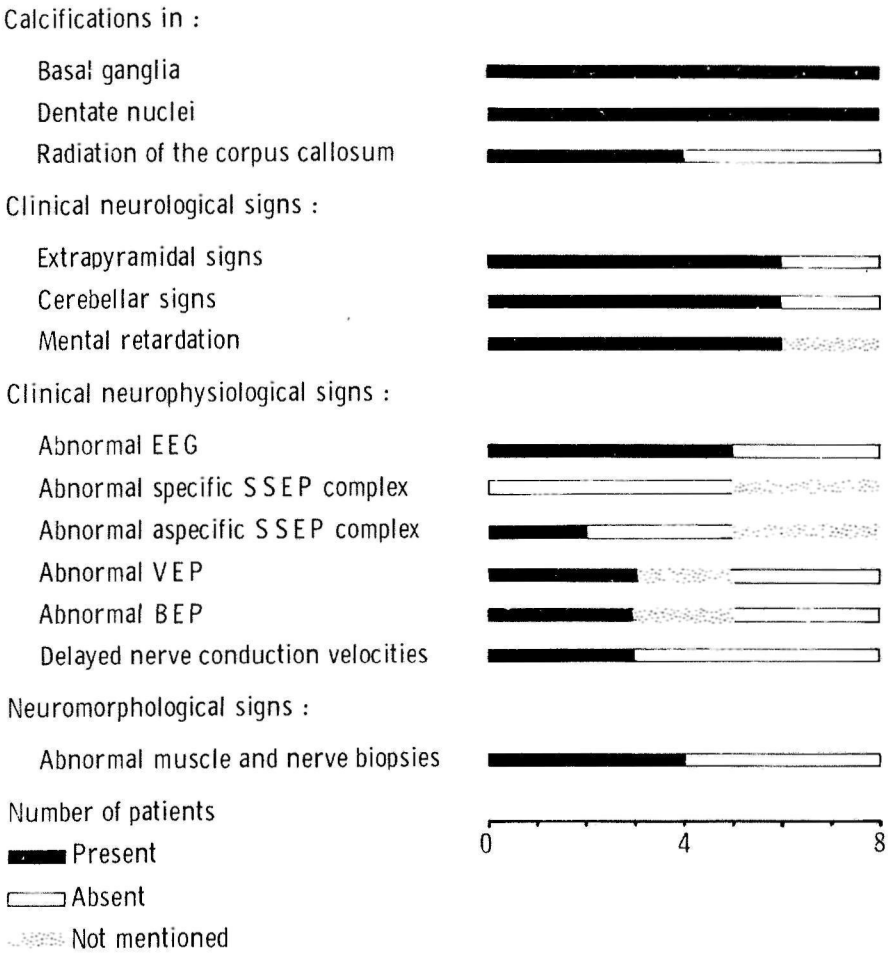

Fig. 2. neuroradiological, clinical neurological, clinical neurophysiological neuromorphological signs in the 8 described patients with familial SPDC.

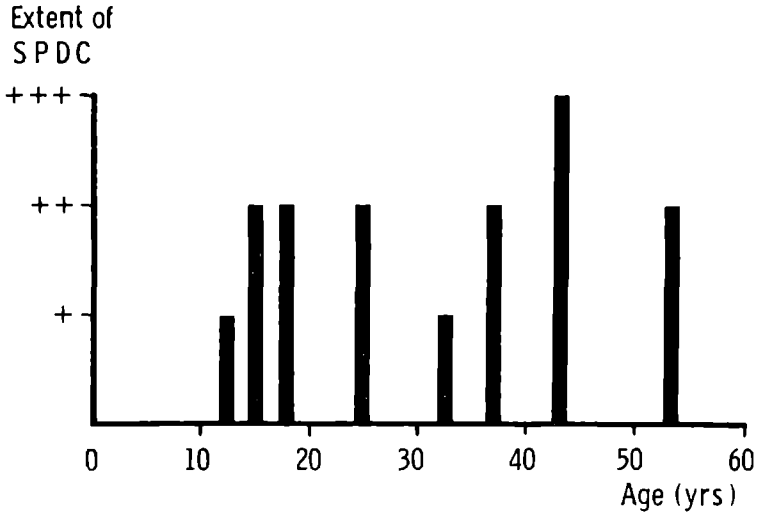

Fig. 3. Representation of the relationship between extent of SPDC and age of the described patients with familial SPDC.

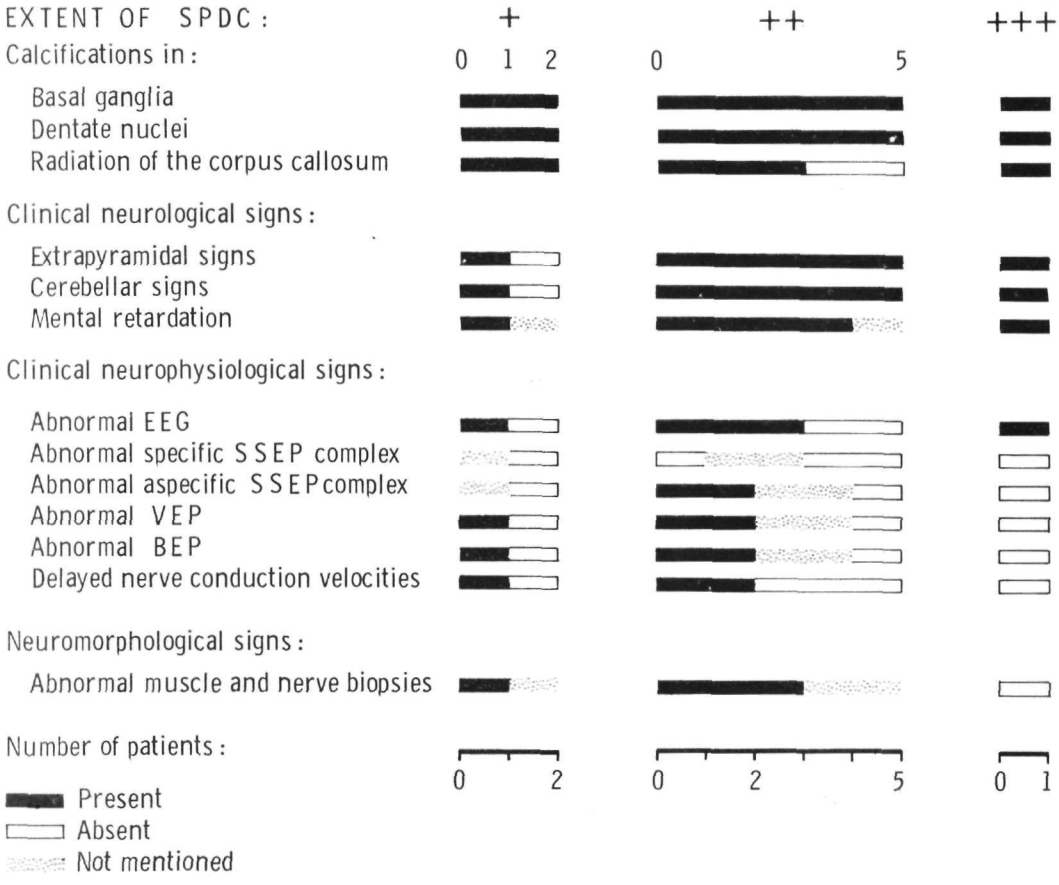

Fig. 4. Neuroradiological, clinical neurological, clinical neurophysiological and neuromorphological signs in groups of patients with familial SPDC showing each SPDC in about similar intensions.

b. Is a disturbance of the Ca-P metabolism involved in the origin of autosomal recessive idiopathic SPDC and Cockayne's syndrome?

In autosomal recessive idiopathic SPDC and Cockayne's syndrome the Ca-P metabolism was studied with the following methods: measurement of the serum concentration of Ca, P, calcitonin, PTH, 25 OH cholecalciferol and 1,25(OH)$_2$ cholecalciferol; determination of the intestinal absorption of calcium; study of the influence of PTH on the renal threshold for phosphate (TmP/GFR); measurement of the calcium and phosphate concentrations in the cerebrospinal fluid (CSF) and examination of radiograms of the hands. In addition, the influence of PTH on the urinary cAMP concentrations was investigated in a patient with Cockayne's syndrome and a patient with autosomal recessive idiopathic SPDC. Using these methods we could not find any disturbance of the Ca-P-metabolism in patients having autosomal recessive idiopathic SPDC and Cockayne's syndrome (chapter VI).

c. Can indications be found for the presence of a cerebral PTH-responsive adenylcyclase complex?

The presence of the renal PTH-responsive adenylcyclase complex can be demonstrated by the administration of PTH. This results in an increased urinary production of cyclic adenosine monophosphate (cAMP) (5).

In order to know if a cerebral PTH-responsive adenylcyclase complex exists, we studied the effect of PTH on CSF cAMP concentrations.

In three healthy adults, PTH produced a 4-7 fold increase in CSF cAMP concentrations while saline injection did not increase CSF cAMP concentrations. (chapter V). This latter finding suggests that PTH-induced CSF cAMP increase is not the consequence of a stress effect. As CSF cAMP is produced in the brain (4), our observations suggest the presence of a cerebral PTH-activated complex that induces cAMP production. In analogy with the renal

PTH-responsive adenylcyclase complex we suggest that this complex is a cerebral PTH-responsive adenylcyclase complex.

d. Is the function of the cerebral PTH-responsive adenylcyclase complex disturbed in autosomal recessive idiopathic SPDC and Cockayne's syndrome?

In a patient with autosomal recessive idiopathic SPDC and in a patient with Cockayne's syndrome we studied the function of the PTH-responsive adenylcyclase complex (chapter VI).
In the patient with autosomal recessive idiopathic SPDC, PTH produced a normal response of CSF cAMP while in the Cockayne's syndrome patient the response was normal.
These findings indicate that the sensitivity of the cerebral PTH-responsive adenylcyclase complex is decreased in autosomal recessive idiopathic SPDC while the PTH-responsive adenylcyclase complex functions normally in Cockayne's syndrome.

7.2.2 Some additional results

In all three patients with autosomal dominant idiopathic hypoparathyroidism (IHPT), epilepsy was the first manifestation of the disease (chapter IV). Two patients showed mental deterioration and strio-cerebellar signs. Their CT-scans revealed calcification of the basal ganglia and dentate nuclei, which seemed to increase during normocalcemia produced by dihydrotachysterol therapy. This indicates that other factors than merely hypocalcemia influenced the cerebral calcifying process.
Somatosensory evoked potential studies, conducted in patients with autosomal dominant IHPT and sporadic IHPT (chapter IV), revealed an abnormal non-specific complex, indicating a dysfunction of the cortical gray matter.
The studies on autosomal dominant IHPT (chapter IV) indicate that in the evaluation of hypoparathyroidism, one must be aware of the possibility of epilepsy, mental deterioration, strio-cerebellar signs, SSEP disturbances and SPDC.

In the family with autosomal recessive idiopathic SPDC the youngest patient had calcifications only in the dentate nuclei and pons, while his elder siblings had additional calcifications in the basal ganglia and radiation of the corpus callosum (chapter II). These latter calcifications were the most pronounced in the eldest. This suggests that in autosomal recessive idiopathic SPDC the calcifying process is progressive. It probably begins in the dentate nuclei and pons and subsequently spreads to the basal ganglia and radiation of the corpus callosum.

In addition, in the siblings with Cockayne's syndrome the extent of the calcifications increased with age, indicating that the calcifying process is progressive. No conclusions can be drawn, however, on the course of this calcifying process.

Reviewing the literature for Cockayne's syndrome (chapter III), we found 96 recorded cases from 66 families. This ratio is in agreement with the hypothesis that Cockayne's syndrome is autosomal recessively inherited. The main symptoms are: a progressive deterioration after a normal development during the first year of life, microcephaly, dwarfism, senile appearance, photosensitive dermatitis, central motor disturbances, SPDC, retinal pigmentation and peripheral neuropathy. Since only 51 percent of the described cases had six or more of these main symptoms, a minimal and unique cluster of diagnostic criteria is not possible. Laboratory investigations have not revealed any consistent abnormalities.

The Cockayne's syndrome siblings, described in chapter III, displayed all these above-mentioned symptoms, except for microcephaly and retinal pigmentation. Studies on brainstem auditory evoked potentials, visual evoked potentials and colorvision showed abnormalities which increased with the age of the siblings and which were consistent with demyelination of the central white matter. Nerve and muscle biopsies revealed a demyelination of the peripheral nerves, which also increased with age (chapter III). The concurrence of a demyelination of the peripheral and central nervous system points to a disturbance of the myelin or myelinating cells, also seen in some

leukodystrophies. Our observations strongly support the theory proposed by Moosa and Dubowitz (11) of Cockayne's syndrome being a leukodystrophy. The increase with age of the neurological disturbances, diagnosed by the neuroradiological, evoked potentials, color vision and electro-neurographical studies, indicates that these non-invasive methods can help evaluate the progression of the disease.

7.3 Discussion

CT-scan studies of the family having siblings suffering from idiopathic SPDC suggested autosomal recessive inheritance. However, it is possible that the apparently unaffected family-members have cerebral calcifications, the degree of which was beyond the detectionlevel of our CT-scanner (see appendix) at the time of the investigation. Neurological studies of the families with autosomal dominant idiopathic hypoparathyroidism, autosomal recessive idiopathic SPDC and Cockayne's syndrome suggest that in these disorders the calcifying process is progressive. Prospective studies with the method described in the appendix may confirm this progression.

CT-scans of the patients with familial SPDC revealed that in addition to calcifications in the strio-pallido-dentate system, other parts of the brain can also be involved in the calcifying process. Subsequently, one must be aware that the name "strio-pallido-dentate calcinosis" may also imply cerebral calcifications outside the strio-pallido-dentate system.

The studies on autosomal dominant IHPT (chapter II) revealed neurological signs, which can be evaluated easily by CT-scan and somatosensory evoked potential studies. These techniques may become useful tools in the evaluation of hypoparathyroidism and its therapy. The presence of a cerebral PTH-responsive adenylcyclase complex (chapter V) raises intriguing questions concerning its location and function. The immediate response of CSF cAMP after stimulation by intravenously injected PTH suggests that PTH (or bioactive fragments of this hormone) can cross the blood-brain barrier to activate an adenylcyclase complex that is in close association with CSF.

The analogy with the renal PTH-responsive adenylcyclase complex suggests that the cerebral PTH-responsive adenylcyclase complex is involved in the regulation of the cerebral Ca-P metabolism.

In the Cockayne's syndrome patients we could not find any disturbance of the Ca-P metabolism, nor could we find any other metabolic disorder (chapter III). The function of the cerebral PTH-responsive adenylcyclase complex seemed to be normal (chapter VI). As our study involved only one patient with Cockayne's syndrome and normal values were obtained from only three persons, a degree of caution is required in making this conclusion. Recently Vos et al (18) found indications of lysosomal pathology in sural nerve biopsies from our and other Cockayne's syndrome patients. It is possible that further studies of lysosomes from Cockayne's syndrome patients could help elucidate pathological factors.

In autosomal recessive idiopathic SPDC, no abnormalities of the Ca-P metabolism could be detected also (chapter VI). However, the decreased sensitivity of the cerebral PTH-responsive adenylcyclase complex, which we noted in the investigated patient (chapter VI), suggests that a defective cerebral PTH-responsive adenylcyclase complex is involved in the etiology of autosomal recessive idiopathic SPDC. As the cerebral PTH-responsive adenylcyclase complex not only seems to be defective in autosomal recessive idiopathic SPDC, but also in autosomal dominant IHPT (see addendum chapter VI), the defect can probably be located at different places in the cerebral PTH-responsive adenylcyclase complex.

It is possible that some of the neurological signs of hypoparathyroidism are produced by hypofunction of the cerebral PTH-responsive adenylcyclase complex. This hypofunction could be produced by the lack of bio-active parathyroid hormone (which occurs in "surgical" hypoparathyroidism and idiopathic hypoparathyroidism) or by a decreased sensitivity of the PTH-responsive adenylcyclase complex (which occurs in pseudo-hypoparathyroidism). We suggest that a defective cerebral adenylcyclase complex is involved in the neurological symptomatology of both familial idiopathic SPDC and hypoparathyroidism. It is probable that the cause of the neurological symptomatology

of these two disorders is not related to the cause of the symptomatology of Cockayne's syndrome.

The way in which the defective PTH-responsive adenylcyclase complex produces SPDC is not known, nor is there any understanding as to why the strio-pallido-dentate system becomes especially calcified.

In SPDC patients many different neurological signs can be present and many different disorders can be diagnosed. This difference in symptomatology does not mean that SPDC has no clinical significance. In view of the fact that few SPDC patients have been described without any neurological sign, we are of the opinion that SPDC is a sign of cerebral dysfunction. Its presence warrants investigation of the Ca-P metabolism, anoxic and toxic factors and familial occurrence. When more is know about the function of the cerebral PTH-responsive adenylcyclase complex, an investigation of this complex in SPDC patients might throw new light on the origin of SPDC.

7.4 Conclusions.

From the results of the studies, presented in this thesis, the following conclusions can be drawn:

I. 1. The neuroradiological sign 'strio-pallido-dentate calcinosis' is a sign of cerebral dysfunction. Its presence warrants investigation of the calcium-phosphate metabolism, axoxic and toxic factors and familial occurence.

2. The familial neuroradiological sign 'strio-pallido-dentate calcinosis' is not associated with a specific complex of neurological signs.

II. 1. Autosomal recessive idiopathic strio-pallido-dentate calcinosis and Cockayne's syndrome are not associated with a disturbance in the calcium-phosphate metabolism.

2. A human cerebral parathyroidhormone-responsive adenylcyclase complex is likely to exist.

3. Dysfunction of the cerebral parathyroidhormone-responsive adenylcyclase complex is probably involved in the etiology of autosomal recessive idiopathic strio-pallido-dentate calcinosis.

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APPENDIX

QUANTIFICATION OF CT SCAN-DIAGNOSED CALCIFICATIONS

M.A.O. Thijssen
M.G. Smits

1. Introduction

The CT-scan is the best method by which to diagnose cerebral calcifications in vivo. Although smaller cerebral calcifications can be detected with this technique than by skull radiograms, it is likely that minute cerebral calcifications cannot be seen. The minimal extent of a calcification, which can be distinguished by the CT scanner, is determined by the detection level of the used scanner. CT scan not only enables the detection of cerebral calcifications but also makes it possible to measure reasonably well the extent of the calcifications. This suggests that it should be possible to measure the amount of calcium in the calcifications. In this appendix we will discuss factors known to influence the detection level of CT scan-diagnosed calcifications. We will also discuss how it could be possible to determine the calcium content of these calcifications.

2. Factors involved in the quantification of CT scan-diagnosed calcifications

The detection of cerebral calcifications by CT scan is determined by the difference in the absorption of roentgen radiation between the calcification and the surrounding tissue. Absorption is characterized by the absorption coefficient μ. This absorption is measured by the CT scanner and is expressed as Houndfield Units (HU) according to the relation

$$HU = \frac{\mu x - \mu a}{\mu a} \times 1000$$

μx = absorption coefficient of the tissue

μa = absorption coefficient of water

The CT scanner transfers these HU into certain intensities of white which are shown on the monitor. Calcification is expressed as the lighter part while brain tissue is darker. The brightness of the monitor picture can be regulated. Subsequently, the detection threshold or discrimination between the two different tissues only depends upon

the properties of the used CT scanner and the definition of that threshold.

It is important to realise how a calcification in a CT scan slice is "seen" by the CT scanner and what the relationship is between the calcium concentration and the associated Houndsfield value.

In order to quantify a CT scan-detected cerebral calcification, we will first discuss the way in which the CT scanner measures a ball-shaped calcification and expresses this calcification in HU (partial volume effect). We will then give a definition of discrimination between two different types of tissue and describe the relevant properties of our Delta-FS scanner. Thirdly, we will describe how the diameter and the density of a barely visible calcification can be determined. Finally, we will discuss how to determine the calcium content of this barely visible calcification. Using these guidelines it will be possible to calculate reasonably well the amount of calcium in a certain calcification.

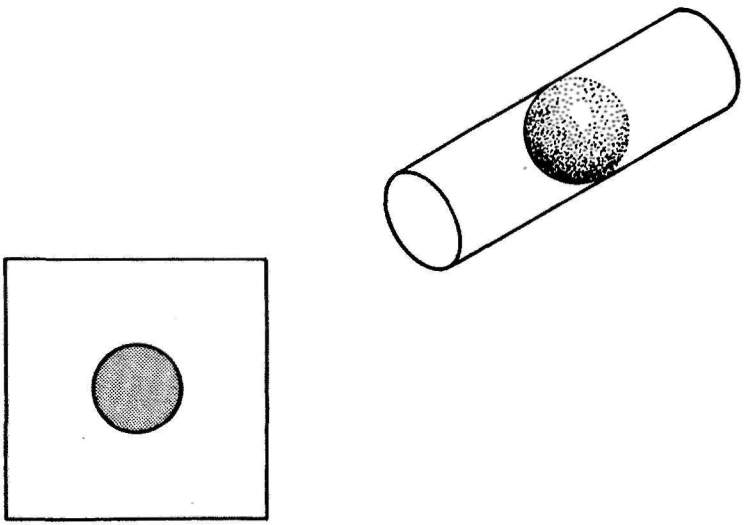

Fig. 1. schematic representation of a ball-shaped particle as "seen" by the CT scan.

a. The partial volume effect.

A ball-shaped particle having a higher absorption than its surrounding tissue can be seen on the CT scan monitor as a bright discus (fig. 1). This thin discus does not represent the absorption of the ball-shaped particle, but it does represent the total absorption of a cylinder with the same diameter as the ball-shaped particle and with a height, which is the same as the slice thickness of the CT scan (fig. 1). Subsequently, the reproduced HU value is the average of the HU value of the ball-shaped particle and the HU value of the rest of the cylinder (partial volume). In formula:

$$HU_{cyl} = \frac{V_{ball}}{V_{cyl.}} HU_{ball} + \frac{V_{cyl} - V_{ball}}{V_{ball}} HU_{surr.}$$

or:

$$HU_{cyl} = \frac{4/3\ \pi r^3}{\pi r^2 h} HU_{ball} + \frac{\pi r^2 h - 4/3\ \pi r^3}{\pi r^3 h} HU\ surr.$$

V_{ball} = Volume of the ball
V_{cyl} = Volume of the cylinder
HU_{cyl} = HU value of the cylinder
HU_{surr} = HU value of the surrounding tissue
r = Radius ball = D/2 = half diameter
h = Height cylinder = slice thickness

When in brain tissue, whose absorption is 35 HU, a ball-shaped particle, whose absorption is 250 HU and whose diameter is 10 mm, is scanned with a slice thickness of 13 mm, this particle is represented as a thin slice with a diameter of about 10 mm and an average absorption of:

$$HU_{cyl} = 35 + \frac{4 \times 5}{3 \times 13} (250 - 35) = 145{,}3\ HU.$$

Thus every measured absorption of a calcification has to be corrected for the partial volume effect. When the diameter of the calcification is more than 13 mm, the exact HU value can be measured directly in the centre of the calcification.

b. Discrimination between two different tissues.

To be able to discriminate between two tissues, the average HU value of one tissue has to differ sufficiently from the other tissue. These values differ sufficiently when the difference between the m1 and m2 values is more than the sum of the standard deviation of both tissue values (fig. 2).

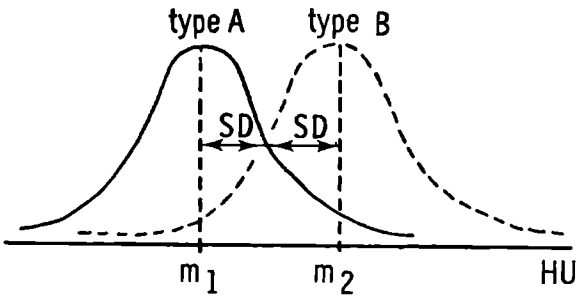

Fig. 2 discrimination between tissue A and B is possible when the difference between m values is more than the sum of the standard deviation (SD) of both tissue values.

Because of the finite exactness of the CT scanner measurements, the average value and the standard deviation depend upon the diameter and density of the particle. Small cylinders have to have higher absorption values to be seen on the monitor, than larger cylinders. The relationship between diameter and density of cylinders which just can be seen, is represented by the contrast-detail curve. Fig. 3 represents the contrast-detail curve of our CT scanner, as it was measured by M.A.O. Thyssen.

Using the contrast-detail curve it is possible to calculate the detection level of the calcification with a certain diameter and a certain maximal HU value. In table 1 the underlined values represent the diameter of a just barely visible calcification with a certain maximal HU value. Any particle with a higher HU value or a greater diameter can be seen with the Delta-FS CT scan.

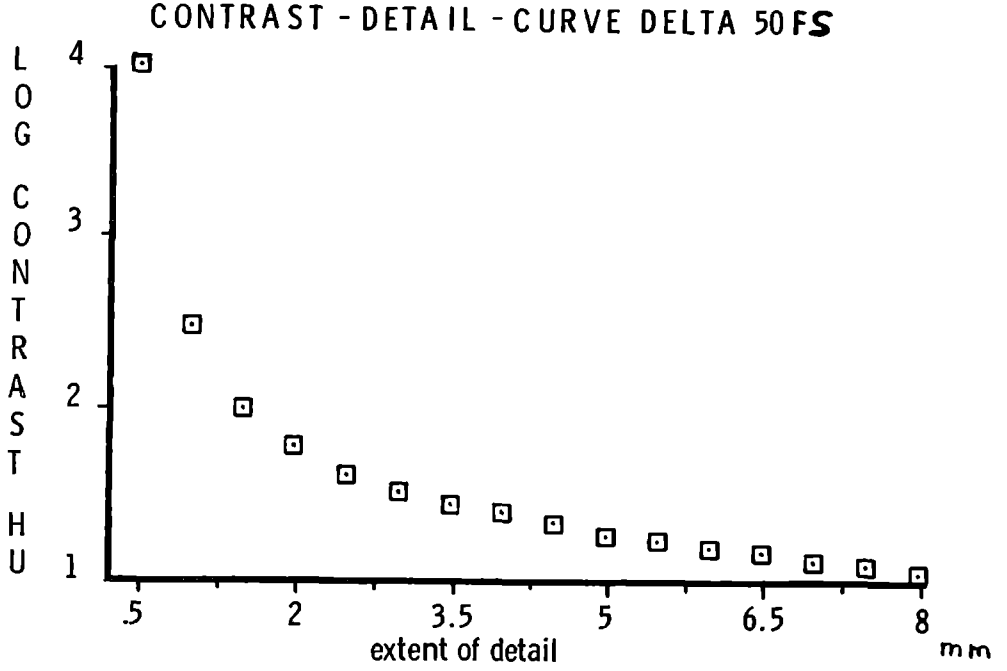

Fig. 3. contrast-detail curve of the Delta FS CT scanner.

c. Determination of the diameter of a calcification.

We have seen that, because of the partial volume effect, a ball with a uniform density is not represented homogenously on the CT scan monitor. The HU value of the ball decreases from the centre to the edge.

Subsequently a certain criterium has to be chosen for the determination of the diameter. Usually the criterium is the "Full width at half maximum" (F.W.H.M.). To calculate this F.W.H.M. (fig. 4) the maximum HU with respect to the surrounding tissue has first to be determined. Next, at the value of half this maximum HU value, the diameter of the calcification is calculated. The advantage of this procedure is that this F.W.H.M. diameter does not depend upon the HU value itself.

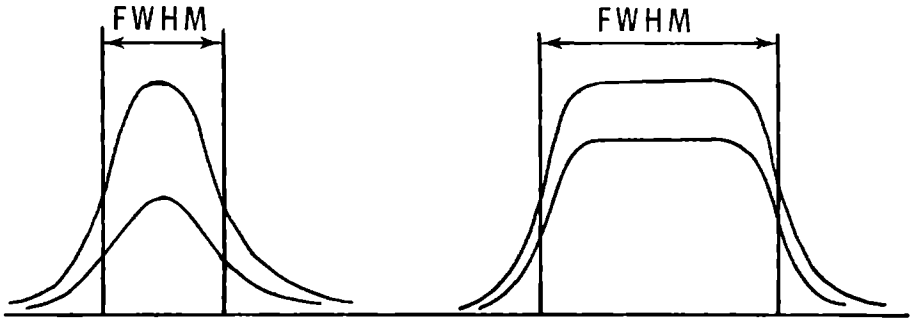

Fig. 4. schematic representation of the "Full width at half maximum" (FWHM)

d. Determination of the amount of calcium.

H. Venema (UVA, Amsterdam) has shown, on theoretical grounds, that there is a direct relation between the HU value of a calcification and its density. He calculated that 1 HU = .41 mg Ca/cc.
In a homogenous ball-shaped calcification with a known diameter and a known HU value, which is corrected for the partial volume effect, the total amount of calcium can be calculated:

$$\text{mg Ca} = 4/3\ \pi\ r^3 \times \frac{1}{.41} \times \text{HU} = \text{Volume} \times \text{concentration.}$$

Table 2 represents the total amount of calcium in a calcification having a known (corrected) HU value.

3. Procedure to estimate the total amount of calcium in CT scan-diagnosed calcifications

With the following procedure it is possible to estimate the total amount of calcium in a calcification "seen" at the Delta-FS CT scan monitor:

1. determine the diameter of the calcification at F.W.H.M.
2. the average HU value of the surface with the in "1" calculated diameter is determined.
3. from table 1 the associated HU value is determined.
4. at the determined diameter and maximum HU value the amount of calcium can be read from tabel 2.

When the diameter of the calcification is greater than the slice thickness, the maximum value in the centre of the calcification can be determined directly.

Cerebral calcifications in the strio-pallido-dentate system are not ball-shaped. However, the above described method provides a reasonably good evaluation of the calcium content of a cerebral calcification.

DIAM. BALL	HU BALL						
	150	200	250	300	350	400	450
.5	37.95	39.23	40.51	41.80	43.08	44.36	45.64
1	40.90	43.46	46.03	48.59	51.16	53.72	56.29
1.5	43.85	47.70	51.54	55.39	59.24	63.09	66.93
2	46.80	51.93	57.06	62.19	67.32	72.45	77.58
2.5	49.75	56.16	62.57	68.99	75.40	81.81	88.22
3	52.70	60.39	68.09	75.78	83.48	91.17	98.87
3.5	55.65	64.63	73.60	82.58	91.56	100.54	109.51
4	58.60	68.86	79.12	89.38	99.64	109.90	120.16
4.5	61.55	73.09	84.63	96.18	107.72	119.26	130.80
5	64.50	77.32	90.15	102.97	115.80	128.62	141.45
5.5	67.45	81.55	95.66	109.77	123.88	137.98	152.09
6	70.40	85.79	101.18	116.57	131.96	147.35	162.74
6.5	73.25	90.02	106.69	123.36	140.04	156.71	173.38
7	76.30	94.25	112.21	130.16	148.12	166.07	184.03
7.5	79.25	98.48	117.72	136.96	156.20	175.43	194.67
8	82.20	102.72	123.24	143.76	164.28	184.80	205.32
8.5	85.15	106.95	128.75	150.55	172.36	194.16	215.96
9	88.10	111.18	134.27	157.35	180.44	203.52	226.61
9.5	91.05	115.41	139.78	164.15	188.52	212.88	237.25
10	94.00	119.65	145.30	170.95	196.60	222.25	247.90
10.5	96.94	123.88	150.81	177.74	204.67	231.61	258.54
11	99.89	128.11	156.32	184.54	212.75	240.97	269.18
11.5	102.84	132.34	161.84	191.34	220.83	250.33	279.83
12	105.79	136.57	167.35	198.13	228.91	259.69	290.47
12.5	108.74	140.81	172.87	204.93	236.99	269.06	301.12
13	111.69	145.04	178.38	211.73	245.07	278.42	311.76

Table 1. Diameter and maximal HU values of cerebral calcifications, calculated for the Delta-FS CT scanner. The underlined values represent the diameter of a just barely visible calcification with a certain maximal HU value.

500	600	700	800	900	1000
46.93	49.49	52.06	54.62	57.19	59.75
58.85	63.98	69.11	74.24	79.37	84.50
70.78	78.48	86.17	93.87	101.56	109.26
82.71	92.97	103.23	113.49	123.75	134.01
94.64	107.46	120.29	133.11	145.94	158.76
106.56	121.95	137.34	152.73	168.12	183.51
118.49	136.45	154.40	172.36	190.31	208.27
130.42	150.94	171.46	191.98	212.50	233.02
142.35	165.43	188.52	211.60	234.69	257.77
154.77	179.92	205.57	231.22	256.87	282.52
166.20	194.41	222.63	250.84	279.06	307.27
178.13	208.91	239.69	270.47	301.25	332.03
190.05	223.40	256.74	290.09	323.43	356.78
201.98	237.89	273.80	309.71	345.62	381.53
213.91	252.38	290.86	329.33	367.81	406.28
225.84	266.88	307.92	348.96	390.00	431.04
237.76	281.37	324.97	368.58	412.18	455.79
249.69	295.86	342.03	388.20	434.37	480.54
261.62	310.35	359.09	407.82	456.56	505.29
273.55	324.85	376.15	427.45	478.75	530.05
285.47	339.34	393.20	447.07	500.93	554.80
297.40	353.83	410.26	466.69	523.12	579.55
309.33	368.32	427.32	486.31	545.31	604.30
321.25	382.81	444.37	505.93	567.49	629.05
333.18	397.31	461.43	525.56	589.68	653.81
345.11	411.80	478.49	545.18	611.87	678.56

DIAMETER BALL (MM)	VOLUME (BALL (MM3)	MAXIMAL HU-VALUE					
.5		150	200	250	300	350	400
.5	0.07	0.02	0.03	0.04	0.05	0.06	0.06
1	0.52	0.19	0.26	0.32	0.38	0.45	0.51
1.5	1.77	0.65	0.86	1.08	1.29	1.51	1.72
2	4.19	1.53	2.04	2.55	3.06	3.58	4.09
2.5	8.18	2.99	3.99	4.99	5.99	6.98	7.98
3	14.14	5.17	6.90	8.62	10.34	12.07	13.79
3.5	22.45	8.21	10.95	13.69	16.43	19.16	21.90
4	33.51	12.26	16.35	20.43	24.52	28.61	32.69
4.5	47.71	17.46	23.27	29.09	34.91	40.73	46.55
5	65.45	23.95	31.93	39.91	47.89	55.87	63.85
5.5	87.11	31.87	42.49	53.12	63.74	74.37	84.99
6	113.10	41.38	55.17	68.96	82.75	96.55	110.34
6.5	143.79	52.61	70.14	87.68	105.21	122.75	140.29
7	179.59	65.71	87.61	109.51	131.41	153.31	175.21
7.5	220.89	80.81	107.75	134.69	161.63	188.57	215.51
8	268.08	98.08	130.77	163.47	196.16	228.85	261.54
8.5	321.56	117.64	156.86	196.07	235.28	274.50	313.71
9	381.70	139.65	186.20	232.75	279.30	325.85	372.39
9.5	448.92	164.24	218.99	273.73	328.48	383.23	437.97
10	523.60	191.56	255.41	319.27	383.12	446.98	510.83
10.5	606.13	221.76	295.67	369.59	443.51	517.43	591.35
11	696.91	254.97	339.96	424.95	509.94	594.92	679.91
11.5	796.33	291.34	388.45	485.57	582.68	679.79	776.91
12	904.78	331.02	441.36	551.70	662.03	772.37	882.71
12.5	1022.66	374.14	498.86	623.57	748.29	873.00	997.71
13	1150.35	420.86	561.15	701.43	841.72	982.01	1122.29

Table 2. amount of calcium in cerebral calcifications with known (corrected for partial volume effect) HU values. The underlined values represent the amount of Ca in just barely visible calcifications.

450	500	600	700	800	900	1000
0.07	0.08	0.10	0.11	0.13	0.14	0.16
0.57	0.64	0.77	0.89	1.02	1.15	1.28
1.94	2.16	2.59	3.02	3.45	3.88	4.31
4.60	5.11	6.13	7.15	8.17	9.19	10.22
8.98	9.98	11.97	13.97	15.96	17.96	19.95
15.52	17.24	20.69	24.14	27.58	31.03	34.48
24.64	27.38	32.85	38.33	43.80	49.28	54.75
36.78	40.87	49.04	57.21	65.39	73.56	81.73
52.37	58.19	69.82	81.46	93.10	104.74	116.37
71.84	79.82	95.78	111.74	127.71	143.67	159.63
95.61	106.24	127.48	148.73	169.98	191.23	212.47
124.13	137.92	165.51	193.09	220.68	248.26	275.85
157.82	175.36	210.43	245.50	280.57	315.64	350.72
197.12	219.02	262.82	306.63	350.43	394.23	438.04
242.44	269.38	323.26	377.14	431.01	484.89	538.77
294.24	326.93	392.32	457.70	523.09	588.48	653.86
352.93	392.14	470.57	549.00	627.43	705.85	784.28
418.94	465.49	558.59	651.69	744.79	837.89	930.99
492.72	547.47	656.96	766.45	875.94	985.44	1094.93
574.68	638.54	766.24	893.95	1021.66	1149.37	1277.07
665.27	739.19	887.02	1034.86	1182.70	1330.53	1478.37
764.90	849.89	1019.87	1189.85	1359.83	1529.81	1699.78
874.02	971.13	1165.36	1359.59	1553.81	1748.04	1942.27
993.05	1103.39	1324.07	1544.75	1765.43	1986.10	2206.78
1122.43	1247.14	1496.57	1746.00	1995.43	2244.86	2494.28
1262.58	1402.86	1683.44	1964.01	2244.58	2525.16	2805.73

SUMMARY

Some aspects of the symptomatology and etiology of familial calcifications in the strio-pallido-dentate system have been studied in a father and his son with autosomal dominant idiopathic hypoparathyroidism, three siblings with autosomal recessive idiopathic strio-pallido-dentate calcinosis (SPDC) and in three siblings with Cockayne's syndrome. Another study was carried out in order to demonstrate the presence of a human cerebral parathyroid-hormone-responsive adenylcyclase complex. After indications were found for its presence, the function of this cerebral PTH responsive adenylcyclase complex was studied in a patient with autosomal recessive idiopathic SPDC and in a patient with Cockayne's syndrome.

The most important results of these investigations are summarized in the following paragraphs.

1. In the patients with autosomal dominant idiopathic hypoparathyroidism the extent of the SPDC increased during normocalcemia. This indicates that other factors than merely hypocalcemia, influence the cerebral calcifying process. In five patients with idiopathic hypoparathyroidism the non-specific complex of the somatosensory-evoked potentials (SSEP) was disturbed. These findings indicate that CT scan and SSEP might contribute to the diagnosis and evaluation of hypoparathyroidism and to its therapy.

2. In the youngest patient with autosomal recessive idiopathic SPDC, the cerebral calcifications were located in the dentate nuclei and pons. His elder siblings had additional calcifications in the basal ganglia and radiation of the corpus callosum. These calcifications were the most extensive in the eldest. These findings suggest that in autosomal recessive idiopathic SPDC the calcifying process is a progressive disorder. It seems to start in the dentate nuclei and pons, and subsequently progresses to the basal ganglia and the radiation of the corpus callosum.

3. The CT scans of the three siblings with Cockayne's syndrome showed calcifications in the basal ganglia and dentate nuclei. Their extent increased with age, suggesting that in Cockayne's syndrome the calcifying proces is progresive. The sural nerve biopsies of the three siblings revealed segmental de- and remyelination with onion bulb formation. Disturbed visual and brainstem auditory-evoked potentials indicated demyelination of the central nervous system. The peripheral and central myelinopathy increased with age, suggesting a progressive disorder. These observations support the theory of Cockayne's syndrome being a leucodystrophy.

4. There was no correlation between the clinical neurological, clinical neurophysiological and neuromorphological signs of the patients with familial SPDC and the extent and location of the cerebral calcifications. This indicates that SPDC is not associated with a specific entity of clinical neurological, clinical neurophysiological, and/or neuromorphological signs.

5. In the siblings with autosomal recessive idiopathic SPDC and in the siblings with Cockayne's syndrome studies on the plasma values of calcium, phosphate, parathyroid hormone, calcitonin, cerebrospinal fluid (CSF) concentrations of calcium and phosphate, intestinal calcium absorption, radiograms of the hands and studies on the influence of parathroid hormone on the renal threshold for phosphate and the urinary cAMP concentrations were conducted. The results revealed no abnormalities suggesting a normal calcium-phosphate metabolism in autosomal recessive idiopathic SPDC and Cockayne's syndrome.

6. In three healthy adults the injection of parathyroid hormone (PTH) produced a four-to-seven fold increase of CSF cAMP concentration. This suggests the presence of a cerebral PTH-responsive adenylcyclase complex.

7. In a patient with autosomal recessive idiopathic SPDC and in a patient with Cockayne's syndrome the influence of PTH on CSF cAMP was studied. In the Cockayne's syndrome patient the response was normal. In the SPDC patient the response was significantly decreased. This finding suggests

that a dysfunction of the cerebral adenylcyclase complex is involved in the etiology of autosomal recessive idiopathic SPDC.

8. The most important conclusions of this thesis are:

I. 1. The neuroradiological sign 'strio-pallido-dentate calcinosis' is a sign of cerebral dysfunction. Its presence warrants investigation of the calcium-phosphate metabolism, axoxic and toxic factors and familial occurence.

2. The familial neuroradiological sign 'strio-pallido-dentate calcinosis' is not associated with a specific complex of neurological signs.

II. 1. Autosomal recessive idiopathic strio-pallido-dentate calcinosis and Cockayne's syndrome are not associated with a disturbance in the calcium-phosphate metabolism.

2. A human cerebral parathyroidhormone-responsive adenylcyclase complex is likely to exist.

3. Dysfunction of the cerebral parathyroidhormone-responsive adenylcyclase complex is probably involved in the etiology of autosomal recessive idiopathic strio-pallido-dentate calcinosis.

FAMILIAIRE STRIO-PALLIDO-DENTALE VERKALKINGEN

Enige klinische en etiologische aspecten

SAMENVATTING

Enige aspecten van de sympomatologie en etiologie van familiare verkalkingen in het strio-pallido-dentale systeem (SPDC) werden onderzocht bij een vader en zijn zoon met autosomaal dominante idiopathische hypoparathyreoidie (IHPT), twee mannen en een vrouw, uit één gezin, met autosomaal recessive idiopathische SPDC en twee jongens en een meisje, uit één gezin, met het syndroom van Cockayne. Tevens werd een onderzoek verricht, om het bestaan van een cerebraal parathormoongevoelig adenylcyclase complex aan te kunnen tonen. Nadat aanwijzingen waren gevonden voor het bestaan hiervan, werd de werking van dit cerebraal parathormoongevoelig adenylcyclase complex onderzocht bij een patiente met autosomaal recessieve idiopathische SPDC en bij een patient met het syndroom van Cockayne.

De belangrijkste resultaten van deze onderzoekingen worden in de volgende paragrafen samengevat.

1. Bij de patienten met autosomaal dominante IHPT nam de grootte van de SPDC toe, terwijl de calcium concentratie in het serum normaal was. Dit wijst erop dat méér factoren, dan alleen een te lage plasma calsium concentratie, invloed hebben op de toename van de SPDC. Bij patienten met autosomaal dominante IHPT en bij 3 andere patienten met sporadische IHPT was het niet-specifieke complex van de somatosensory evoked potentials (SSEP) abnormaal. Deze bevindingen wijzen erop dat CT scan en SSEP onderzoeken een bijdrage kunnen leveren aan de diagnostiek en de evaluatie van hypoparathyreoidie, terwijl deze onderzoeken mogelijk ook een bijdrage kunnen leveren aan de evaluatie van de therapie van dit ziektebeeld.

2. Bij de jongste patient met autosomaal recessieve idiopathische SPDC bevonden de verkalkingen zich in de nuclei dentati en de pons, terwijl zijn oudere broer en zus bovendien verkalkingen hadden in de basale ganglia en radiatio van het corpus callosum. Deze verkalkingen waren het grootst bij de oudste patiente. Deze bevindingen suggereren dat bij autosomaal recessieve idiopathische SPDC de verkalkingen het eerst ontstaan in de nuclei dentati en pons, terwijl in een later studium ook verkalkingen ontstaan in de basale ganglia en de radiatio van het corpus callosum.

3. De drie patienten met het syndroom van Cockayne hadden allen verkalkingen in de basale ganglia en de nuclei dentati. Bij de jongste waren deze verkalkingen het kleinst, bij de oudste het grootst. Dit wijst erop dat de SPDC toeneemt bij patienten met het syndroom van Cockayne. Nervus suralis biopten van de drie kinderen met het syndroom van Cockayne lieten segmentale de- en remyelinisatie met onion-bulbs zien, terwijl gestoorde visual- en brainstem auditory-evoked potentials wezen op demyelinisatie in het centrale zenuwstelsel. Deze perifere en centrale demyelinisatie nam toe met de leeftijd van de patienten. Dit suggereert dat de demyelinisatie bij het syndroom van Cockayne progressief is. De bevindingen steunen de theorie, dat het syndroom van Cockayne behoort tot de groep van leudodysstrofieën.

4. Bij de patienten met familiaire SPDC konden wij geen verband aantonen tussen de aanwezigheid van cerebrale verkalkingen en het optreden van bepaalde klinisch neurologische, klinisch neurofysiologische en/of neuromorfologische verschijnselen. Dit wijst erop dat SPDC niet gepaard gaat met een kenmerkend klinisch neurologisch, klinisch neurofysiologisch en/of neuromorfologisch symptomen complex.

5. Bij patienten met autosomaal recessieve idiopathische SPDC en bij patienten met het syndroom van Cockayne waren de plasma concentraties van calcium, fosfaat, parathormoon, calcitonine en de liquor concentraties van calcium en fosfaat normaal. Ook de intestinale calcium absorptie, rontgenfoto's van de handen en het effect van parathormoon op de nierdrempel voor fosfaat en op de cyclisch AMP concentratie in de urine waren ongestoord.

Deze bevindingen wijzen erop dat het calcium-fosfaat metabolisme bij autosomaal recessieve idiopathische SPDC en het syndroom van Cockayne niet gestoord is.

6. Bij drie gezonde proefpersonen veroorzaakte de intraveneuze toediening van parathormoon een vier- tot zevenvoudige toename van de liquor cyclisch AMP concentratie. Dit suggereert de aanwezigheid van een cerebraal parathormoon gevoelig adenylcyclase complex.

7. Het functioneren van het cerebraal parathormoon-gevoelig adenylcyclase complex werd onderzocht bij een patient met het syndroom van Cockayne en bij een patient met autosomaal recessieve idiopathische SPDC. Bij de patient met het syndroom van Cockayne veroorzaakte parathormoon een normale toename van de liquor cyclisch AMP concentratie. Bij de patiente met autosomaal recessieve idiopathische SPDC steeg de liquor cyclisch AMP concentratie onvoldoende. Deze bevindingen suggereren dat het cerebraal parathormoon-gevoelig adenylcyclase complex normaal functioneert bij het syndroom van Cockayne, terwijl bij autosomaal recessieve idiopathische SPDC de functie hiervan gestoord is. Mogelijk speelt een verminderde gevoeligheid van het cerebraal parathormoon gevoelig adenylcyclase complex een rol bij het ontstaan van autosomaal recessieve idiopathische SPDC.

8. De belangrijkste konklusies van dit proefschrift zijn:

I. 1. Neuroradiologisch aantoonbare strio-pallido-dentale verkalkingen wijzen op een gestoorde hersenfunctie en kunnen aanleiding geven tot onderzoek naar stoornissen in de calcium-fosfaat stofwisseling, anoxische en toxische faktoren en naar een familiair voorkomen van deze verkalkingen.

2. Familiair voorkomende neuroradiologisch aantoonbare strio-pallido-dentale verkalkingen gaan niet gepaard met kenmerkende neurologische verschijnselen.

II. 1. Autosomaal recessieve idiopathische strio-pallido-dentale verkalkingen en het syndroom van Cockayne gaan niet gepaard met een gestoorde calcium-fosfaat stofwisseling.

2. In de menselijke hersenen bevindt zich waarschijnlijk een voor parathormoon gevoelig adenylcyclase complex.
3. Een stoornis in het cerebrale parathormoon-gevoelig adenylcyclase-complex is vermoedelijk betrokken bij het onstaan van autosomaal recessieve idiopathische strio-pallido-dentale verkalkingen.

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De aanzet voor de hier gepresenteerde studie werd gegeven door drs. J.J. Prick, tijdens mijn stage "klinische en poliklinische neurologie" in het Canisius Wilhelmina Ziekenhuis te Nijmegen. Verder onderzoek werd verricht vanuit de Afdeling Kinderneurologie (Hoofd: Prof. Dr. F.J.M. Gabreëls) van het Instituut voor neurologie (Hoofd: Dr. B.P.M. Schulte) van het Sint Radboud Ziekenhuis te Nijmegen.

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CURRICULUM VITAE

De auteur van dit proefschrift werd op 10 januari 1952 in Eindhoven geboren. Van 1964 tot 1970 volgde hij daar het Gymnasium β aan het gymnasium Augustinianum.

In 1970 begon hij de studie geneeskunde aan de Katholieke Universiteit te Nijmegen. In 1973 werkte hij 3 maanden als student-assistent in het Will Rogers Reasearch Center te Saranac Lake U.S.A. (hoofd Dr. D. Hospelhorn). Hierna werkte hij 10 maanden als student-assistent op de afdeling Fysiologie (hoofd Prof. Dr. S.J.A. Kreuzer) van de Faculteit der Geneeskunde. In 1978 werd het artsexamen afgelegd.

Na het artsexamen werkte hij 3 maanden als algemeen arts in het psychiatrisch ziekenhuis Huize Padua te Boekel. Daarna volgde hij de opleiding tot neuroloog aan het St. Radboud Ziekenhuis te Nijmegen (opleider Prof. Dr. B.P.M. Schulte). De stage psychiatrie werd gevolgd in het Diakonessenhuis te Arnhem (opleider Dr. Th.B. Kraft). Op 1 oktober 1982 werd hij ingeschreven in het specialisten register.

Sinds 1 oktober 1982 is hij als neuroloog werkzaam in het Juliana Ziekenhuis te Ede en sinds 1 april 1983 tevens als kinderneuroloog in het Centrum voor kinderen met ontwikkelingsstoornissen en kinderpsychiatrie "De Ederhorst" te Ede.

Sinds 1 oktober 1983 volgt hij de opleiding voor de aantekening klinische neurofysiologie aan het St. Radboud Ziekenhuis te Nijmegen (opleiders Prof. Dr. S.L.H. Notermans en Drs. P.H.J. Bernsen).

STELLINGEN

Behorende bij het proefschrift

FAMILIAL STRIO-PALLIDO-DENTATE CALCINOSIS

SOME CLINICAL AND ETIOLOGICAL ASPECTS

In het openbaar te verdedigen
op 2 maart 1984
des namiddags te 4 uur

door

M.G. SMITS

I

Verkalkingen in het strio-pallido-dentale systeem wijzen op een functiestoornis van de hersenen.

- dit proefschrift.

II

Verkalkingen in het strio-pallido-dentale systeem gaan niet gepaard met kenmerkende neurologische verschijnselen.

- dit proefschrift.

III

Dierexperimenteel onderzoek zal informatie kunnen geven over de functie en localisatie van het cerebrale, parathormoongevoelige, andenylcyclase-complex.

- dit proefschrift.

IV

Het is zinvol verder onderzoek te verrichten naar de functie van het cerebrale, parathormoongevoelige, adenylcyclase-complex bij patienten met verkalkingen in het strio-pallido-dentale systeem.

- dit proefschrift.

V

Het syndroom van Cockayne is een vorm van leukodystrofie.

- Moosa en Dubowitz: Arch. Dis. Child. 45:674-677; 1970.

VI

Elke patient met een onbegrepen mentale retardatie heeft recht op een uitvoerig neurologisch onderzoek.

VII

Elke diagnostische ingreep die geen therapeutische consequenties heeft, is een wetenschappelijk onderzoek of experiment en dient te worden omgeven met alle daarbij behorende reserves en maatregelen.

- Robin E.R.: J.A.M.A. 240:2273-2275, 1978.

VIII

Het is zinvol bij iedere patient met onbegrepen epileptische verschijnselen de concentratie van calcium en fosfaat in "nuchter afgenomen" bloed te bepalen.

- Guberman A. Epilepsia 20:541-553, 1979.

IX

Bij de diagnostiek van vaatwandleasies in de halsarteriën heeft intraveneuze digitale subtractie-angiografie in het algemeen de voorkeur boven conventionele catheter angiografie.

- de Vries A.J.R. Proefschrift, Amsterdam 1984.

X

Therapie bij metabole spierziekten dient voorafgegaan te worden door uitvoerige moleculaire diagnostiek.

XI

Het kennen van variaties in de normale psycho-motore ontwikkeling van het kind is onmisbaar bij het herkennen van een gestoorde ontwikkeling.

XII

Kinderen met onbegrepen leerstoornissen hebben recht op uitvoerig didactisch, neuropsychologisch en kinderneurologisch onderzoek.

XIII

Het "promoveren op artikelen" dient krachtig gestimuleerd te worden.

XIV

Het blijft een onopgeloste vraag of verkalkingen in de gezondheidszorg vaker voorkomen dan verkalkingen in de hersenen.